CONTROLLED EXTENDED RELEASE OF ETORICOXIB FOR COLON TARGETING BY USING MULTIPARTICULATE SYSTEM

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The Tamil Nadu Dr. M.G.R. Medical University, Chennai

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MASTER OF PHARMACY

(Pharmaceutics)

Submitted by

LIMCE THAMPI

Under the guidance of

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COIMBATORE – 641 044

Certificate

This is to certify that the dissertation entitled **"CONTROLLED EXTENDED RELEASE OF ETORICOXIB FOR COLON TARGETING BY USING MULTIPARTICULATE SYSTEM"** was carried out by **LIMCE THAMPI** in the Department of Pharmaceutics, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, which is affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, under my direct supervision and guidance to my fullest satisfaction.

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ACKNOWLEDGEMENT

It gives me immense pleasure in submitting my dissertation ***"CONTROLLED EXTENDED RELEASE OF ETORICOXIB FOR COLON TARGETING BY USING MULTIPARTICULATE SYSTEM"***

It was a matter of great pride that I was fortunate enough to have association with great personalities.I can remember their names only with profound gratitude and satiety.

"No work is accomplished, with optimum refinement, support and indulgence of others"

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CONTENTS

INTRODUCTION

MICROCAPSULES [1]

Microcapsules are small particles of solids or small droplets of liquids surrounded by a wall of natural polymer and also synthetic polymer films of varying thickness and degree of permeability in the size range of about 0.1-1000μm. The purpose for microencapsulation are environmental protection gastric irritation reduction, liquid-solid conversion ,taste–odour masking separation of incompatibilities, controlling sustaining action of active substances minimizing and eliminating side effects.

Microencapsulation provides many possibilities for producing improved forms of pharmaceutical and diagnostic aids. History of micro encapsulation says ***CREATION OF LIVING CELLS IS THE BEGINNING OF MICRO ENCAPSULATION***. Most of the one celled animals are living examples of micro encapsulation.

CONTROLLED–RELEASE DRUG-DELIVERY [2,3,4,5,6,7]

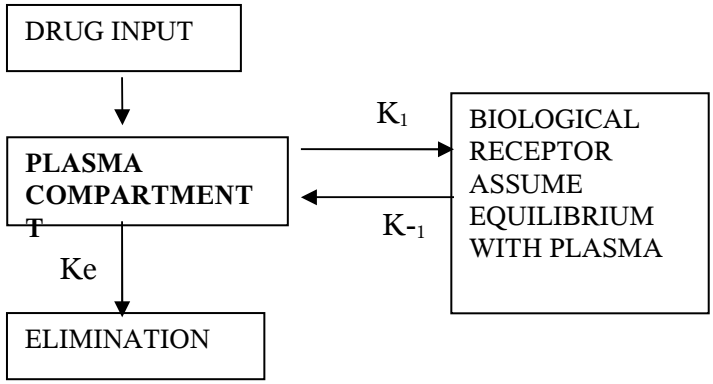
The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. That is, the drug- delivery system should deliver drug at a rate dictated by the needs of the body over a specified period of treatment. This idealized objective points to the two aspects most important to drug delivery, namely, *spatial placement and*

temporal delivery of a drug .Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed controlled - release drug – delivery system can be a major advance toward solving these two problems. It is for this reason that the science and technology responsible for development of controlled- release pharmaceuticals has been, and continues to be the focus of a great deal of attention in both industrial and academic laboratories.

In the recent years, considerable attention has been focused on the development of new drug delivery systems. The therapeutic efficiency and safety of drugs administered by conventional methods can be improved by more precise spatial and temporal placement within the body, thereby reducing both the size and number of doses, through a controlled drug delivery.

In the simplest model (Figure 1) the fate of the drug may be characterized by a single compartment, which is described by the plasma concentration of drug with time.

Figure 1 A simple pharmacokinetic model[3]



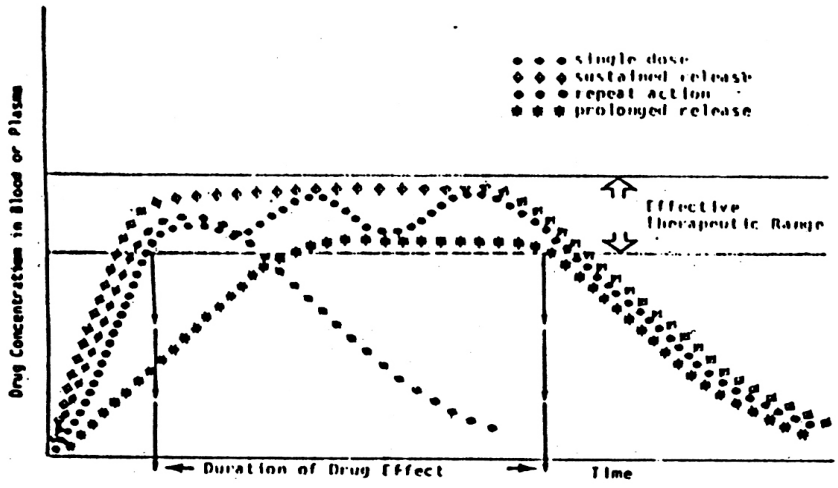
Controlled-release drug delivery produce a well-characterized and reproducible dosage form that controls drug entry into the body within the specifications of the required drug delivery profile. Conventional tablets fails in the lack of characterization and control of absorption.

DEFINITION AND TERMINOLOGY

Delivery rates from temporal controlled release system may be characterized in terms of their kinetics and physical processes of particular interest are zero order systems for which the release of drug is constant with time. Zero order systems can be in principle allow for selection of precise. Efficacious plasma levels after titration for inter-individual variation with a controlled constant drug input, greater selectivity of drug action and reduced toxicity might be achieved by avoiding successive peaks and valleys of drug concentration associated with conventional therapy. This concept of plasma steady state or zero-order pharmacology will have far reaching implications in the ultimate goal of optimum drug therapy.

Unfortunately, there is no universal agreement in the use of such terms, the products designed to provide an extended duration of action in comparison to single dose can be classified into three main categories. Figure 2

Figure 2 Different plasma release profiles resulting from various extended duration products[4-6]



1. Sustained-release products

These are drug delivery systems designed to provide an initial therapeutic dose that is made available upon administration, followed by maintenance of activity over an extended period of time.

2. **Prolonged release products:**

This term refers to preparation designed to provide a slow release of a drug at a rate which will provide a longer duration of action in comparison to the normal single dose. Prolonged release products may show a relatively delayed onset of action due to their overall slow release rate

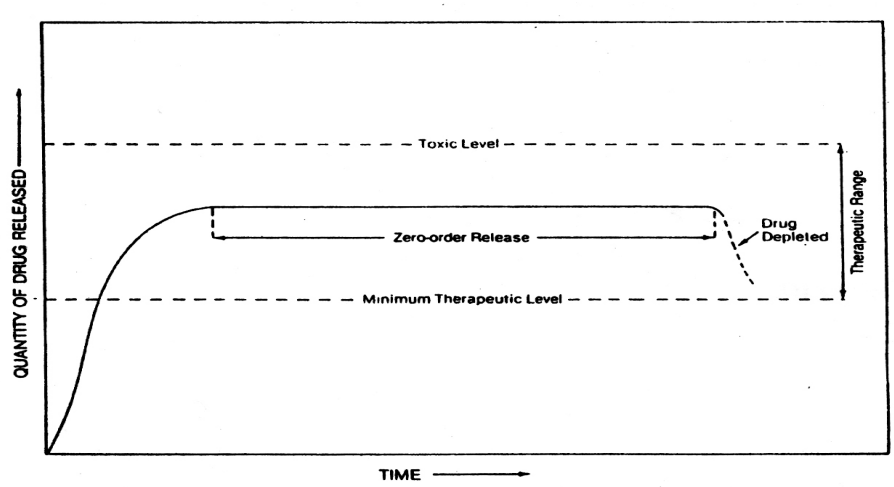
3. **Repeat action preparations:**

These are products designed to release an initial dose immediately after administration, followed by a second and a third dose after the same period of time has elapsed.

CLASSIFICATION OF CONTROL DRUG DELIVERY SYSTEM

Controlled (Zero- order) drug release is schematically illustrated in Figure 3

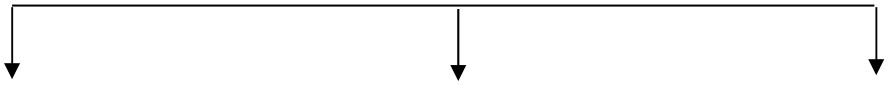
Figure 3 Schematic Illustration of Controlled drug release[7]



Drug concentration levels in the blood plasma are not necessarily equal to the quantity of drug released from a device because drug absorption is determined largely by its solubility in tissues and availability of local blood flow in the tissues. Even if the drug concentration in plasma were to remain reasonably constant, small short-term fluctuations would always be seen due to factors such as physical activities, emotional stimulation (stress), eating and sleeping.

The design and fabrication of oral CR systems are reviewed under the following classification.

Oral controlled release system



a. Dissolution control
   a. Intestinal release
b. Diffusion control
c. Dissolution and diffusion control based system.
d. Ion- exchange resins
e. Osmotically controlled devices
f. Slow dissolving salts or complexes
g. PH-independent formulations

b. Size- based systems

a. Density based systems
b. Colonic release
c. Bio-adhesive based systems

ADVANTAGES AND DISADVANTAGES

The goal of oral CR products is to achieve better therapeutic success than with conventional dosage forms of the same drug. This goal is realized by improving the pharmacokinetic profile as well as patient convenience and compliance in therapy. This improvement is perhaps the major reason for so much attention being focused on drugs used in chronic therapy.

The complexity of the variable and regulations involved in the manufacture of drug products necessitates that a careful risk and benefit

analysis should be conducted before a final decision is made to develop a controlled release product.

ADVANTAGES OF EXTENDED RELEASE PRODUCTS.

From the therapeutic point of view extended release products provide three main advantages.

1. Elimination of peaks and valleys in plasma levels so that drug concentration is maintained constant over a long period of time. This is highly desirable in case of antibiotics, anticonvulsants, hypoglycemic and hypotensive agents and number of other medicinal agents used in the treatment of chronic ailments.
2. Long acting products enforce patient compliance due to convenience of dosing regimen i.e., only two tablets or capsules a day instead of one or two every four to six hours.
3. Oral CR formulations are valuable for maintaining plasma levels within a narrow therapeutic range. In fact a valid rationales for formulating drugs with half life of over 8 hours as CR formulation is to maintain plasma drug levels within a narrow therapeutic range. By reducing the rate of drug release, it is possible to produce a flatter plasma-level curve and avoid toxic drug concentration in the body.

DISADVANTAGES OF EXTENDED RELEASE PRODUCTS

Controlled release products must be viewed as multidose preparations, which bear the following consequences of their use.

1. Overdose or dose dumping

Being multidose preparation there is always the possibility of sudden release of the total dose administered, which may result in some toxic manifestations or side effects.

2. Loss of flexibility in dosage

It is very difficult to adjust the dose of extended release product to the patient's response. In many cases an induction of therapy needs to be achieved by a single dosing regimen followed by careful monitoring while under a treatment with extended release preparations.

3. Side effects

Extended duration of action also produce long duration of side effects, especially if the patient happens to be hypersensitive to the given medication.

CHOICE OF DOSAGE FORM [8,9,10,11]

After careful evaluation of a drug candidate for potential formulation in to an extended release product, the decision with respect to the choice of an optimal drug delivery system is determined by the following factors.

1. **Physical and Chemical properties of drug**

The physical and Chemical properties of the drug includes stability, solubility, partitioning characteristics, its ability to form stable insoluble derivatives or salts, its interaction with coating materials or polymeric matrices and other potential incompatibilities.eg. Absorption of poorly soluble drug is often dissolution rate limited and are not good candidates of oral CR formulations drugs with good aqueous solubility make good candidate for CR dosage forms.

2. Desired extension of duration

Obviously a drug product intended to release the active ingredient over a period of days cannot be formulated in an oral dosage form, simply because of the motility of the GIT. Only controlled release products designed to release their content of active ingredient within 12-24 hours can be formulated in a dosage form suitable for oral administration.

3. **Total dosage administered**

In spite of the fact that a lower dose may be needed for a controlled release product as compared to single dosing regimen, extended duration products are multi dose preparation and therefore the total mass of drug included in the formulation may determine the type of dosage form for a given site of action.

4 Route of administration

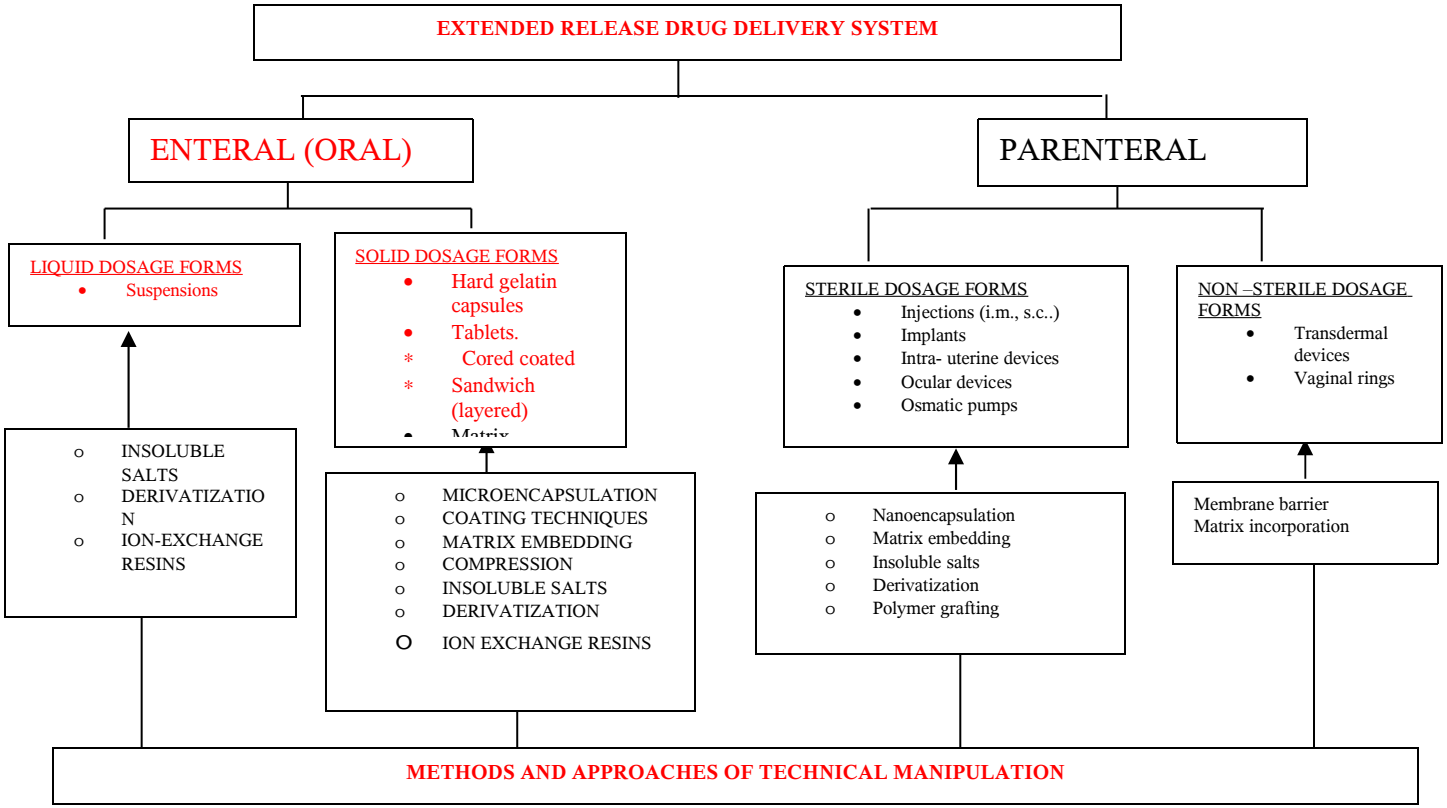
Generally speaking the route of administration determines the type of drug delivery system and therefore the manipulative process of choice. A general classification is extended release drug delivery systems and the most appropriate manipulation technique are shown in figure 4.

Limitations

Not all drugs tend themselves to the formulation of an extended duration product. The most important factors to be considered in choice of drug candidate for controlled release preparation are as follows :

- Biological half life
- Therapeutic dose
- Blood levels and pharmacological activity
- Stability the wide pH range GI enzymes and flora.
- First - pass metabolism

Figure 4 Extended release dosage forms and corresponding methods of technical manipulation[4]



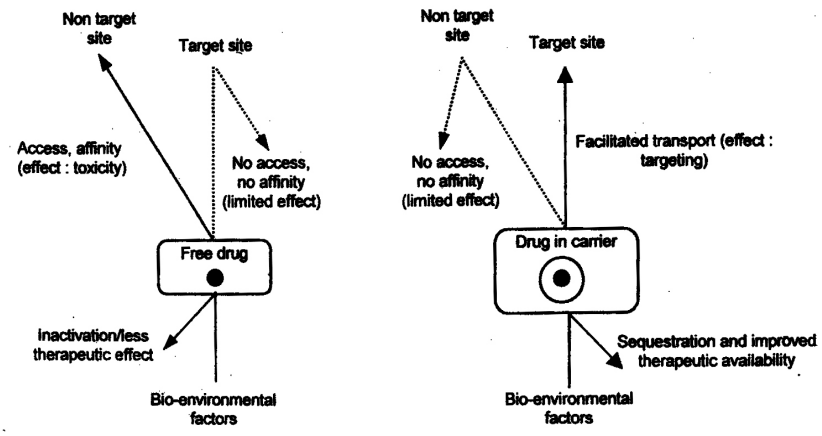
TARGETED DRUG DELIVERY [15]

The principle behind targeted drug delivery system is to obtain a desirable therapeutic effect, i.e. the correct amount of drug should be transported & delivered to the site of action with subsequent control of drug input rate. By targeted drug delivery, we can get improve therapeutic efficacy, reduction in side effects & optimized dosing regimen.

CONCEPTS OF TARGETING

The concepts of designing specified delivery system is to achieve selective drug targeting has been originated from the perception of Paul Ehrlich, who proposed drug delivery to be as a "magic bullets" describing targeted drug delivery as an event where, a carrier-complex/conjugate, delivers drug exclusively to the pre selected target cells in specific manner.

Figure 5 Principle and Rationale of drug Targeting

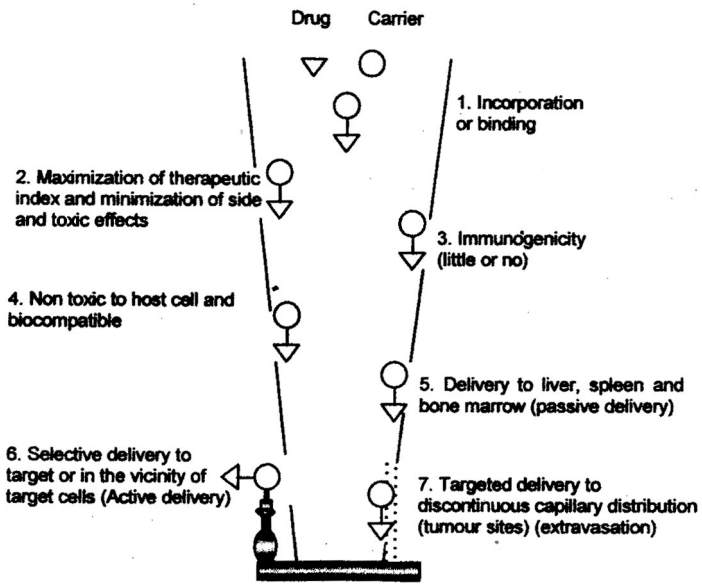


Target is signified if target compartments are distinguished from other compartments, where toxicity may occur & if active drug could be predominantly placed in the proximity of target site.

CARRIERS

Carriers are one of the most important entities essentially required for successful transportation of the loaded drugs. They are drug vectors, which sequester, transport & retain drug enroute, which elute or deliver within or in the vicinity of the target carriers can do so utilities through inherent characteristics or acquired, to interact selectively & biological targets or otherwise they are engineered to release the drug in the proximity of target cells lines demanding optimal pharmacological action (therapeutic index).

Figure 6 Schematic Illustration of the requirement of carriers



Based on nature of their origin, they are categorized as endogenous (low density lipoprotein, high density lipoprotein, chylomicrons, serum albumin, erythrocytes) & exogenous (microparticulate, soluble polymeric & biodegradable polymeric drug carriers)

LEVELS OF DRUG TARGETING

The various approaches of vectoring the drug to the target site can be broadly classified as

1. Passive targeting
2. Inverse targeting
3. Active targeting (ligand medicated targeting& physical targeting)
4. Dual targeting
5. Double targeting
6. Combination targeting.

ADVANTAGES

1. The drug should be transported & delivered to site of action.
2. The control of drug input rate.
3. The target oriented drug administration with improvements of therapeutic efficiency
4. Reduction in side effects.
5. Optimized dosing regimen.

6. Target drug delivery implies for selective & effective localization of pharmacologically active moiety at pre identified targets.
7. Restricted distribution of parent drug to non target site with effective accessibility to target sites.

DISADVANTAGES

1. Rapid clearance of targeted systems especially antibody targeted carriers.
2. Immune reactions against intravenous administered carrier systems.
3. Target tissue heterogeneity
4. Problems of insufficient localization of targeted system into tumor cells.
5. Down regulation & sloughing of surface epitopes
6. Diffusion & redistribution of released drug leading to non-specific accumulation.

COLON DRUG DELIVERY[16]

The colon drug delivery has a number of important implications in the field of pharmacotherapy. Various diseases including Inflammatory Bowel Diseases (IBD) can be effectively treated by the local delivery of drugs to the large intestine. By this technique, absorption of the drug from the stomach and small intestine can be minimized until the drug reaches the large intestine. The treatment of large intestine disorders, such as Crohn's disease, irritable bowel syndrome, colitis, colon cancer and local infectious disease were a high concentration of active drug is needed, can be improved by colon specific drug delivery systems employing various mechanism of release Table 1. The disease state can also potentially alter the delivery and absorption characteristics of drug from the colon.

Table 1 Colon Targeting disease,drug and sites

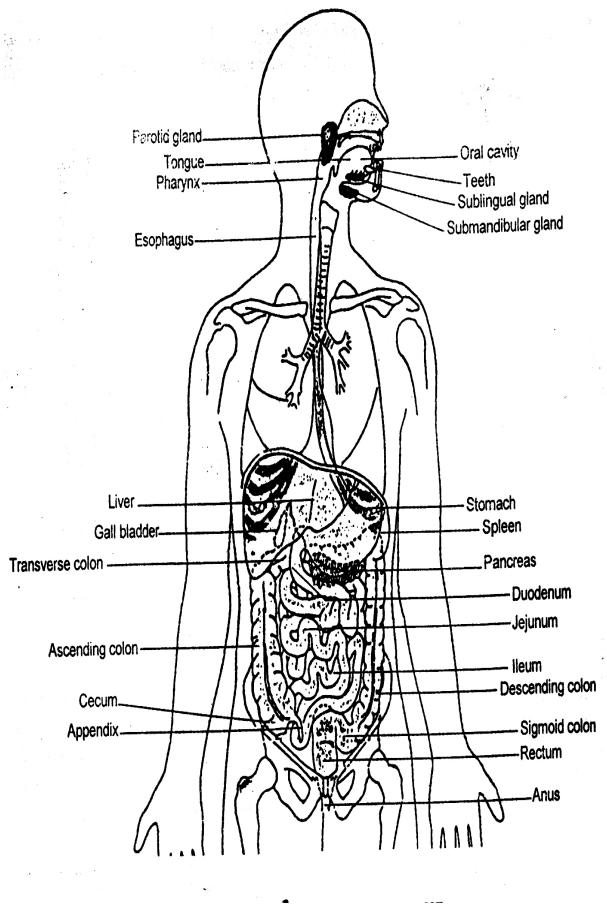
Target sites	Diseases condition	Drugs and active agents
Topical action	Inflammatory Bowel disease, irritable bowel disease and Crohn's disease	Hydrocortisone, Budenoside, Prednisolone, sulfasalazine, Olsalazine, Mesalzine and Balsalazide
Local action	Chronic pancreatitits, pancreatomy and cystic fibrosis ,colorectal cancer	Digestive enzyme supplements 5- Flourouracil
Systemic	To prevent gastric irritation	NSAIDs

action	To prevent first pass Metabolism of orally ingested drugs Oral delivery of peptides Oral delivery of vaccines	Steroids Insulin Typhoid

ANATOMIC AND PHYSIOLOGICAL CONSIDERATIONS FOR COLONIC DRUG DELIVERY

Irrespective of therapy desired for local (colonic) or systemic delivery of drug, the development and aim of the drug delivery to colon, remains same. Firstly, the drug must not be absorbed from other regions of GIT. Thirdly, it should, only suffer negligible degradation in the small intestine lumen. Secondly, the release of the drug in colon should be at quantitatively controlled rate and the released drug should be absorbed from the lumen of the large intestine without any appreciable degradation in the lumen. In order to meet these priories, a thorough knowledge of the anatomy and physiology of GIT is required. Figure 7 and Table 2 categorically presents some important properties of human GIT.

Figure 7 Schematic Representation of Human GIT



In GIT large intestine starts from the ileocecal junction to the anus with a length of about 1.5 m (adults) and is divided into three parts ,viz.,colon, rectum and the anal canal. The colon consists of cecum, colon ascendens, colon transvesale, colon descendens and sigmoid colon. Colon is made up of four layers, serosa, mucularis

externa, submucosa and mucosa. The serosa is the exterior coat of the large intestine and consists of areolar tissue that is covered by a single layer of squamous mesothelial cells. The muscularis externa is composed of the major muscular coat of the inner circular layer of fibers that surrounds the bowel and an outer longitudinal layer. Colonic longitudinal muscle fibers are composed of three flat long bands called taenia coli, which is shorter than other coats of the colon and hence results in wall contractions and formation of haustra. The submucosa is the layer of connective tissue that lies immediately beneath the mucosa lines the lumen of the colon and is divided into epithelium, lamina propria and muscularis mucosae. The blood capillaries and lymphatic vessels supply biofluids to lamina propria.

Table 2 Properties of GIT

Properties of GIT	**Measured values**	**Microbial metabolic and enzymatic reactions in human GIT**
Surface area		
Total GIT	$2\text{-}10^6$ cm^2	Hydrolysis of glucuronides, hydrolysis of glycosides, Hydrolysis
Resting volume	25-50ml	of -CO-NH-compounds (amide,
Stomach	500-700 cm	glycine Conjugates and N-acetyl
Length	20-30 cm	compounds), hydrolysis of esters
Total GIT	150-250 cm	Hydrolysis of sulfamates,
Duodenum	200-350 cm	dehydroxylation (C-dehydroxylation
Jejunum	90-150 cm	(O-demethylation, N-demethylation
Ileum		and other)dehalogenation,
Colon		hetrocyclic ring fusion, reduction of
pH	1-3:5	double bonds, reduction of double
Stomach	5-7	bonds, reduction of nitro group,=s,
Duodenum	6-7	reduction of azogroups, reduction of
Jejunum	7	aldehydes, reduction of ketones,

Ileum Colon Rectum	5.5-7 7	reduction of alcohols, reduction of N-oxides, reduction of aresenic acids aromatization, nitrosamine formation, acetylation & estrification

FACTORS GOVERNING THE COLON DRUG DELIVERY

PHYSIOLOGICAL FACTORS

Gastrointestinal Transit

The drug delivery systems first enter into stomach and small intestine via mouth and then reach colon. The nature and pH of gastric secretions and gastric mucosa influence the drug release and absorption. In order to successfully reach colon in an intact form, the drug delivery system should surpass the barriers in the stomach and small intestine.

Small Intestinal Transit

Normally, the small intestinal transit is not influenced by the physical state, size of the dosage form and the presence of food in the stomach. The mean transit time of the dosage form is about 3-4 h.

Colonic Transit

The bioavailability of drugs, released from the dosage forms can be highly influenced by the colonic transit time. Various factors like gender and size of the dosage form, and physiological conditions such as stress, presence of food and disease state influence the colonic transit time.

Gastric Emptying

Generally, in fasted state, gastric emptying is fastest and most consistent. Emptying completes from 5-10min upto 2 hours, depending on the phase of the stomach at the time of the drug administration. Gastric emptying can be considerably slowed by fed state.

Stomach and Intestinal pH

Generally, the release and absorption of orally administered drugs are influenced by the gastrointestinal pH. The pH gradient in the GIT is not in an increasing order. In stomach the pH is 1.5-2 and 2-6 in fasted and fed conditions, respectively. The acidic pH is responsible for the degradation of various pH sensitive drugs and enteric coating may prevent it. In small intestine, the pH increases slightly from 6.6-7.5 and decreases to 6.4 in right colon.

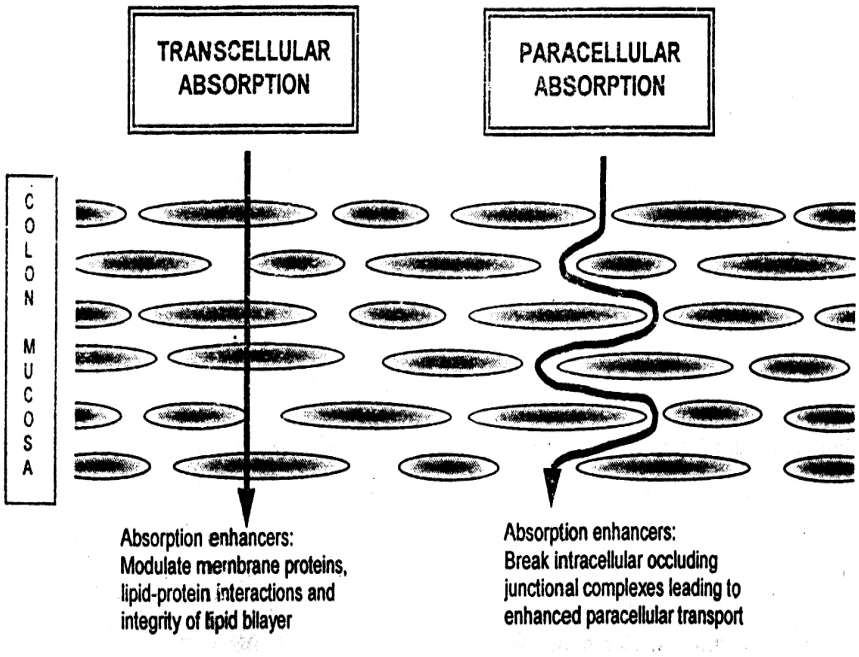
The pH of mid colon and left colon is 6.6 and 7.0 respectively. Since there is minimal variation in the pH from ileum to colon, apparently pH dependent polymer drug delivery may not be much selective.

Colonic Absorption

The surface area of the colon is much less compared to small intestine, and hence not ideally suited for absorption. Despite this limitation, the colon is considered for drug delivery because the environment is devoid of endogenous digestive enzyme other than

from microbial origin and residents time of colon can be as long as 10-24 hours.

Figure 8 Absorption of drugs from colon and mechanism of absorption enhancers.



Drug molecules pass from the apical to basolateral surface of the epithelial cells by figure 8

1. Passing through colonocytes (transcellular transport),or
2. Passing between adjacent colonocytes (paracellular transport)

Gastrointestinal disease state

General intestinal diseases such as IBD, Crohn's disease, constipation, diarrhea and gastroenteritis may affect the release and absorption properties of colon –specific drug delivery systems, Table 3. Most of the diseases associated with nausea and vomiting may expel the drug content. In antibiotic- related colitic condition, plaque formation on the mucosa may interfere with the absorption of drugs.

Table 3 GIT Diseases which affects the Performance of Colon-Specific Drug Delivery Systems

Inflammatory Bowel Diseases (Crohn's disease and ulcerative colitis)	Diarrhea, fever, anemia, obstruction of lymphatic drainage and hyperplasia of lymphoid tissue, which are observed in this condition may affect the drug release and absorption. The inflammatory response extends from mucosa to serosa through intestinal wall. Impairment of lymphatic drainage causes malabsorption of fats and highly lipophilic dings. Thickening of mucosa and submucosa may reduce surface area and obstruct diffusion.
Diarrhea	Hypermotility and frequent passage of hypertonic liquid feces significantly affect drug absorption and release.
Antibiotic associated colitis	Overgrowth of Clostridium difficile and its toxin production, which alters mucosal surface area, may reduce drug absorption.
Constipation	Decreased peristaltic movement of bowel decreases diffusion and availability of drug in absorption sites. Severe constipation reduces bowel movement once or twice a week and interferes with the movement of formulations.
Gastroenteritis	Diarrhea due to increased mucosal secretion may affect the performance of formulations
GIT infections	Diarrhea due to colonic protozoal and

	bacterial infections causes extremely low transit time and increased mucus production, interferes with localization of drug and absorption. Toxins produced may obstruct diffusion process

PHARMACEUTICAL FACTORS

Drug candidates

Drugs, which show poor absorption from the stomach or intestine including peptide drugs, are most suitable for colon specific drug delivery systems. The drugs used in the treatment of IBD, ulcerative colitis, diarrhea and colon cancer, are ideal candidates for local colon delivery.

Drug Carriers

The selection of carrier for particular drug candidate depends on the physicochemical nature of the drug as well as the disease for which the system is to be used. The factors such as chemical nature, stability and partition coefficient of the drug and the type of absorption enhancer chosen influence the carrier selection.

TARGETING APPROACHES TO COLON

Polymer Based Approaches

Biodegradable Matrix and Hydrogel Systems

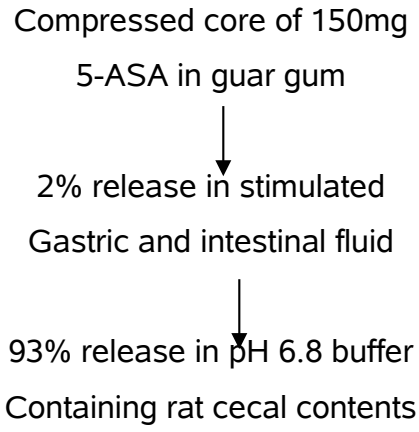
The inability of GIT enzymes to digest certain plant polysaccharides is taken as an advantage to develop colon-specific drug delivery systems. The drug is embedded in the matrix core of the biodegradable polymer by compressing the blend of active drug, a degradable polymer and additives. Various polysaccharides such as

pectin, guargum, chondrotine, etc. are being employed for colon targeting.

pH sensitive polymer system

The mechanism of pH sensitive systems resembles the enteric coating of drugs which prevent drug release in stomach whereas releases the contents in intestine and thus causes a delayed release. The ideal pH sensitive polymers in Table 4 for colon drug delivery are able to withstand the acidic pH of stomach and proximal part of small bowel, and selectively disintegrate the intestinal pH, preferably in ileocecal junction. This process eventually avoids distribution of drug throughout the large intestine and improves the efficacy of colon delivery systems.

Figure 9 Schematic representation of biodegradable Guargum Matrix System



Eudragit polymers are being used for development of colon drug delivery systems. Eudragit-LO and Eudragit SO are soluble at

pH 6 and 7, respectively, hence they are used to make acid-resistant film coating. These polymers were used to develop systems containing drugs such as salsalzine, insulin and quinolones.Eudragit SO coated systems showed optimal delivery of insulin in ileum at pH 7 and successfully delivered more than 60% of sulphapyridine in colon. Partially methylated Eudragit-SO that is soluble in slightly higher pH aqueous media, can be effective for colon drug delivery.

Table 4 Some Properties of pH Sensitive and Biodegrable Polysaccharides

pH sensitive polymers	**Biodegradable polysaccharides**		
Polymer	**Threshold** pH	**Polysaccharides and its general use**	**Bacterial species that degrade polysaccharide**
HPMC phthalate	4.6-4.8	Amylose (tablet excipient)	Bacteroides
PVA Phthalate 50	6.0	Arabinogalactase (thickening agent)	Bifidobacterium
HPMC phthalate 50	5.2	Arabinogalactase (thickening agent)	Bifidobacteria
HPMC phthalate 55	6.4	Chitosan (absorption enhancing agent)	Bacteroides
Eudragit L - 100	6.6	Chitosan (absorption enhancing agent)	Bacteroides
Eudragit L	6.0	Chodroitin sulphate	Bacteroides
Eudragit S	6.8	Pectin (thickening agent)	Bifidobacterium, Eubacterium
Shellac	7.2	Pectin (thickening agent)	Bifidobacterium, Eubacterium
CA Trimellitate	4.8	Dextran (plasma expander) Guar gum (thickening agent) Xylan (Plant hemicellulose)	Bacteroides Bacterioides, Ruminococcus Bacteroides Bifidobacterium

Biodegradable Polymer Systems

The degrading property of enzymes produced by microflora of the colon, particularly azoreductase activity is taken as an advantage in developing bacteria- biodegradable polymer coated drug delivery systems. These systems deliver drugs to colon without releasing drugs in small intestine.

Bioadhesive Polymer Systems

When a system is coated with bioadhesive polymer it adheres on the wall of GIT increases the residence time of the system, there by improving the absorption possibilities. Bio adhesive systems made up of various polymers such as polycarbophils, polyurethanes and polyethylene oxide – polypropylene oxide copolymers showed better adhesion in vitro and to some extent in vivo.

Prodrug Based Approaches

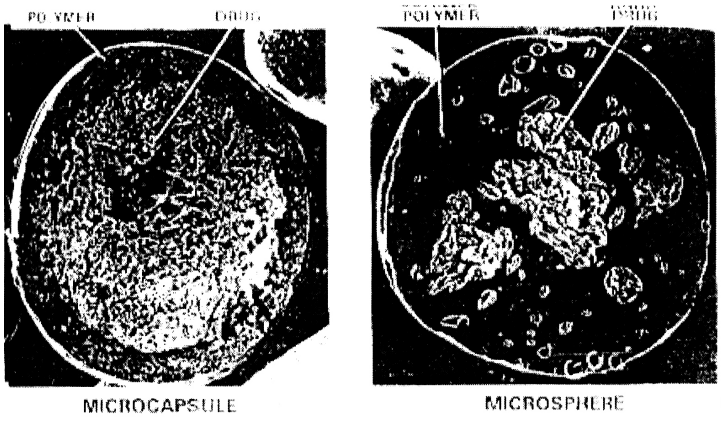
A prodrug is a pharmacologically inactive derivative of a parent compound that requires spontaneous or enzymatic transformation within the body in order to release active drug and that has improved release properties over the parent compound. Prodrug can be designed to release drugs systematically in specific organs and tissues such as kidneys, brain, eyes, breast and skin. The choice of carrier is largely determined by the functional groups available on the drugs.

MICROPARTICULATE DRUG DELIVERY SYSTEMS[2,17,18,19,20]

Microencapsulation techniques have emerged in the past 63 years, following the discovery of complex coacervation of gelatin by Bungenberg de Jong and Kaes. The first commercial application of encapsulation was by the National Cash Register Company for the manufacture of carbon less copying paper.

Microencapsules developed for use in medicine consist of a solid or liquid core material containing one or more drugs enclosed in coating. Microencapsules are often described by other terms such as coated granules, pellets or seeds, microspherules and spansules. The most common type of microencapsules structure is mononuclear spherical.

Figure 10 Structure of Microcapsule and Microsphere



The term 'Microcapsule' should be reserved for reservoir type devices where as 'microsphere' are monolithic or matrix type microparticles. The particles can be embedded with in a polymeric matrix in a solid aggregate state or a molecular dispersion to form microspheres. The particles can be coated by a solidified polymeric develop to form microcapsules as shown in figure 10

Microspheres

-monolithic, uniform distribution of particles or a molecular dispersion.

Microcapsules contain,

- Liquid contents, non- permeable, rigid membrane.
- Aqueous contents, semi permeable membrane.
- solid core, protective or release- controlling coating.

Custom Microencapsulation Design

- Broad size range of capsules: 100nm to 6mm
- Broad range of pay load: upto 95 percent.

CORE MATERIAL

The core material, defined as the specific material to be coated, can be liquid or solid in nature. The composition of core material can be varied, as the liquid core can be including dispersed or dissolved material. The solid core can be a mixture of active constituents, stabilizers, diluents, excipients and release rate retardants or

accelerators. The ability to vary the core material composition provides definite flexibility which enables design and development of desired microcapsule properties.

COATING MATERIAL

Selection of the appropriate coating material dictates, to a major degree, the resultant physical and chemical properties of the micro capsules. The coating material should be capable of forming a film that is cohesive with the core material; be chemically compatible and non reactive with the core material; and provide the desired coating properties such as strength, flexibility, impermeability, optical properties and stability.

Typical coating property such as cohesiveness, permeability, moisture sorption solubility, stability and clarity must be considered in the proper selection of microcapsule coating material. The effective coating thickness varies from tenths of a micron to a few hundred microns depending on the coating-to-core ratio and the particle size of the core material.

Examples of Shell Material

- Proteins
- Polysaccharides
- Starches
- Waxes

- Fats

PURPOSE OF MICROENCAPSULATION

The process of microencapsulation enables as to achieve,

a. Taste-making

b. Selective sorption

c. Sustained release

d. Reduced gastric irritation

e. Conversion of liquid to solid form for stabilization

f. Reduction of volatility

g. Stabilization to oxidation

The final product form can **be *dry powder, tablet, capsule, dispersion, lotion or injectable*.**

METHODS OF MICROENCAPSULATION

Microencapsulation methods that have be or are being adapted to pharmaceutical use include,

1. Co acervation-phase separation

This technique of microencapsulation can be induced by

a. temperature changes

b. *incompatible polymer addition*

c. non-solvent addition

d. polymer-polymer interaction

2. Air suspension

3. Spray drying and spray congealing

4. Pan coating

5. Solvent evaporation

6. Polymerization

7. Physical methods

a. Multi-orifice centrifugal process

b. Electrostatic encapsulation

Southwest Research Institute (SwRI) having more than 50 years of experience in microencapsulation and controlled release, has classified the methods of microencapsulation as;

Physical Methods of Encapsulation	➢ Spray drying ➢ Spray chilling ➢ Rotary disk atomization ➢ Fluid bed coating ➢ Stationary nozzle coextrusion ➢ Centrifugal head coextrusion ➢ Submerged nozzle coextrusion ➢ Pan coating ➢ Phase separation ➢ Solvent evaporation ➢ Solvent extraction
Chemical methods of Encapsulation	➢ Interfacial polymerization ➢ Simple and complex coacervation ➢ In-situ polymerization ➢ Liposome technology

- Nanoencapsulation

TECHNOLOGY INVOLVED IN DIFFUSION TYPE RELEASE SYSTEMS

In these systems the release rate of drugs is determined by its diffusion through a polymer. There are basically two types of diffusion devices: reservoir devices, in which a core of drug is surrounded by a polymeric membrane, and matrix devices, in which drug is distributed uniformly in an inert polymeric matrix. Microspheres represent matrix type drug delivery systems whereas micropellets represent reservoir type systems.

Theoretically, controlled release of drugs from both capsule and matrix type drug delivery systems are controlled by *Fick's law of diffusion* which defines the flux of diffusion J_d across a plane surface of unit area.

$$J_d = - D \, d_c/d_x$$

Where,

dc = diffusion of drug molecule in a medium of solid

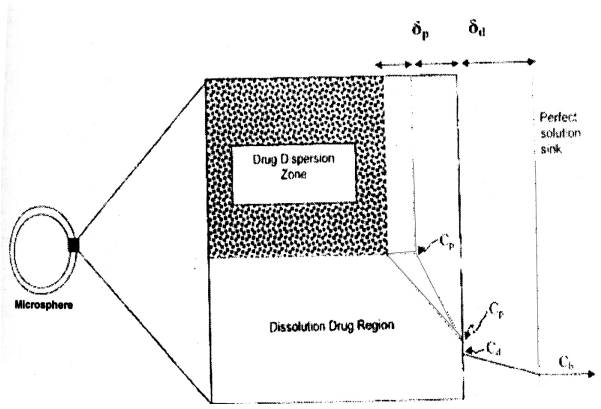
d_c/d_x = concentration gradient of drug molecules across a diffusion path of thickness d_x

The negative sign is used to define the flux of the drug in the action of decreasing the concentration. In the matrix type of drug very systems, the concentration gradient is time dependent and decreases

progressively in response to the growing thickness of diffusional d_x as time goes on. In these systems, the drug molecules can elute out matrix through dissolution and then by diffusion through the polymer structure.

It is observed that dry solid in the layer close to the surface of the device are the first to elute and followed by that in the next layer. This is as shown in the figure 11 below.

Figure 11 Schematic Illustration of Controlled Release of Drug Molecules from Matrix type Drug Delivery Systems



Where,

A = initial amount of drug solids impregnated in a unit volume of polymer matrix

Cp = Solubility of drugs in polymer phase

Cp = Concentration of the drug at the polymer-solution interface

C = Concentration of the solution in bulk of the elution solution

δp = Thickness of drug depletion zone in the matrix

δd = Thickness of hydrodynamic diffusion layer device on the immediate surface.

δ(δp) = Differential thickness of depletion zone formed after more drug solid elutes out.

In this model, it is assumed that the solid drug dissolves from the surface layer first; when this layer becomes exhausted of the drug, the next layer begins to be depleted by dissolution and diffuses through the matrix to the external solution. In this fashion, the interface between the regions was containing the dissolved drug and that containing the dispersed drug moves into the interior as a front.

Higuchi equation

This equation can be used to express the release rate from such systems.

$$Q = \frac{DE}{T(2A - ECS)Cst} x1/2$$

Q = Drug released in g/ unit surface area

D =Diffusion coefficient of the drug

E = Porosity of the matrix

T =Tortousity of the matrix

Cs = Solubility of the drug in the release medium (g/ml)

A = Concentration of the drug in the dosage form

Keeping all the parameters constant, Higuchi equation can be reduced to

$$M = kt^{1/2}$$

Where, K is a constant.

The assumptions made in deriving the mathematical model are,

- A pseudo – steady state is maintained during release
- The total volume of the drug present per unit volume in the matrix is substantially greater than the saturation solubility of the drug per unit volume in the matrix i.e., excess solute is present.
- Drug particles are much smaller in diameter than the average distance of diffusion.
- The diffusion coefficient remains constant
- No interaction occurs between the drug and the matrix.

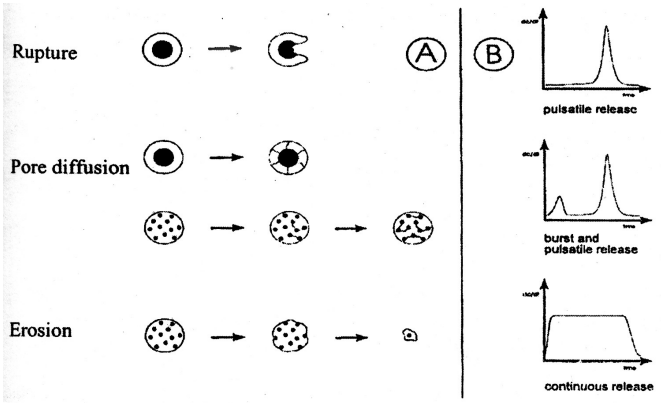
MECHANISM OF DRUG RELEASE FROM MICROPARTICLES

Drug release from degradable micro spheres might give hints on the microstructure of particles and mechanism of erosion. The drug release is influenced by the structure of micro particles and properties of the biodegradable polymer itself.

Most of the drug delivery through microparticles exhibits a matrix type internal solid dispersion morphology structure. The drug may be insoluble in the solid matrix and the drugs are released by a mechanism that involves both pore diffusion and polymer erosion.

Initially water diffuses into the matrix dissolving the drug particles adjacent to the surface. The resulting osmotic pressure is relieved by forming a tarteous channel to the surface and releasing a defined amount of drug in the initial drug burst.

Figure 12 Release of drug from microspheres.



The burst effect is controlled mainly by 3 factors,

1. Drug polymer ratio
2. Particle size of dispersed drug
3. Particle size of microspheres.

As the penetrating water front continues to diffuse into a micro particulate core , the dispersed drug particles are dissolved, creating a network of water filled pores through which the drug diffuses in a controlled manner, and hence the name, pore diffusion.

From gel beads, leakage of drug can occur as influenced by polymer concentration and mechanical treatments of beads. Physical

shaking produces more leakage than packed beads in a column. The open lattice structure, although a disadvantage in allowing leakage of small proteins, does provide high porosity for large substrates and efficient exchange of substrates and products. The polymer may be cross linked with chitosan, polyacrylic acid, polyvinyl alcohol, protein and polyethylenimine to produce more stable, lower porosity complexes with improved leakage characteristics.

DELIVERY SYSTEMS FOR MICROSPHERES.[21]

For commercial use, microspheres should be placed in pharmaceutically acceptable oral delivery systems which include tablets, capsules and dry powders for reconstitution into suspension. The former two are the most widely used oral systems, but pose significant technological challenges to the delivery of microspheres. Tablets are prepared by compression of spheres, and the compression forces may deform and fuse the microspheres rendering them into larger aggregates. Compression forces and heat generated during compression may affect the stability of the encapsulated drug.

A capsule formation although providing more favorable manufacturing conditions, could lead to chemical instability since capsule shells are made up of gelatin or starch. To maintain flexibility, they maintain up to 12% moisture which may promote chances for hydrolytic cleavage of the biodegradable polymer. While filling into

capsules or compression into tablets, minimize fragmentation and fusion of particles as both effects may alter the release properties.

BIODEGRADABLE POLYMERS AS CARRIERS FOR CONTROLLED RELEASE

The different types of biodegradable polymers for extended release preparations are given below.

- Natural

  Albumin Collagen

  Starch Chitosan

  Dextran Casein

  Gelatin Hemoglobin

  Fibrinogen

- Synthetic

  Poly (alkyl-cyanocrylate)

  Poly (ethyl-cyanocrylate)

  Poly (amino acids)

  Poly (amides)

  Poly (acryl amides)

  Aliphatic Polyesters

  Poly (malic acid)

  Poly (glycolic acid)

  Poly (hydroxyl butyrate)

Poly (lactic acid)

Cross Linked Proteins and Hydrogels

Poly Vinyl Alcohols (PVA)

Cross-linked Poly Vinyl Pyrrolidone (PVP)

NON-BIODEGRADABLE POLYMERS

Poly Ethylene Vinyl Acetate

Poly Ether Urethane (PEU)

Cellulose Acetate (CA)

Poly Vinyl Chloride (PVC)

MICROSPHERE PREPARATION BY SOLVENT EVAPORATION METHOD [22]

A wide range of microencapsulation techniques have been developed to date. The selection of the technique depends on the nature of the polymer, the drug, and the intended use. Pharmaceutically acceptable microencapsulation techniques using hydrophobic biodegradable polymers as matrix material are divided into four categories.

1. Emulsion-solvent evaporation (o/w, w/o, w/o/w)]
2. Phase separation (non solvent addition and solvent partitioning)
3. Interfacial polymerization
4. Spray drying

The solvent evaporation methods involves the emulsification of an organic solvent (usually methylene chloride) containing dissolved polymer and dissolve/ dispersed drug in an excess amount of aqueous continuous phase with the aid of an agitator. The concentration of the emulsifier present in the aqueous phase affects the particle size and shape. When the desired emulsion droplet size is formed, the stirring rate is reduced and evaporation of the organic solvent is realized under atmospheric or produced pressure at an appropriate temperature. Subsequent evaporation of the dispersed phase solvent yields solid polymeric microparticles entrapping the drug. The solid microparticles are recovered from the suspension by filtration, centrifugation or lyophilization. Phase separation is a non-aqueous method that is suitable for encapsulation of water-soluble and water-insoluble drugs, generally used for encapsulation of peptides and proteins. In interfacial polymerization a capsule shell is formed at or on the surface of a droplet or particle by polymerization. Spray drying is used to protect sensitive substances from oxidation based on the atomization of solution by compressed air and drying across a current of warm air.

SOLVENT EVAPORATIONPROCESS

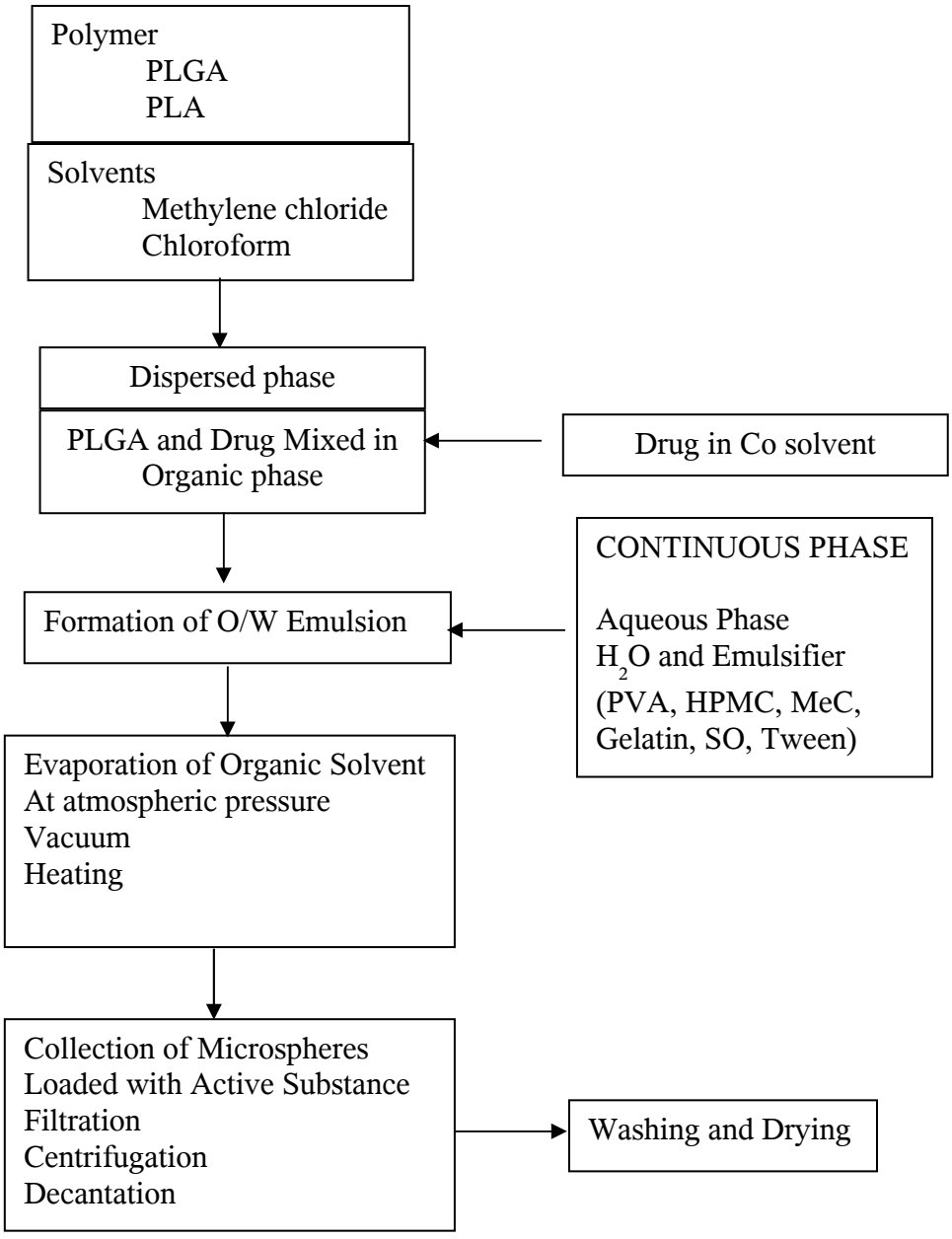
Single –Emulsion Solvent Evaporation

1. O/W Emulsion Solvent Evaporation Technique

For emulsion solvent evaporation, there are basically two systems from which to choose: oil- in- water (o/w) or water- in- oil (w/o). Oil- in – water emulsions are more widely used than w/o emulsions due to the simplicity of the process and easy clean- up requirements for the final product. In this process, both the drug and the polymer should be insoluble in water, while a water- immiscible solvent is required for the polymer. A schematic representation of o/w emulsification- solvent evaporation technique is shown in Figure 13

In general, solvent evaporation method is particularly suitable for the microencapsulation of lipophilic drugs that can be either dispersed or dissolved in the dispersed phase of a volatile solvent.

Figure 13 Schematic representation of the preparation of PLGA microspheres by o/w emulsification/solvent evaporation technique



2. Oil- in-oil emulsification- solvent evaporation technique

The major problem of the o/w emulsification technique is the low encapsulation efficiency of moderately water- soluble and water-insoluble compounds. The drug can diffuse from the organic dispersed phase into the aqueous continuous phase, which results in poor entrapping. Water- soluble drugs such as, theophylline, caffeine, and salicylic acid could not be loaded efficiently using an o/w emulsion method, whereas drugs with low water solubility such as diazepam, hydrocortisone, and progesterone were successfully entrapped in microspheres.

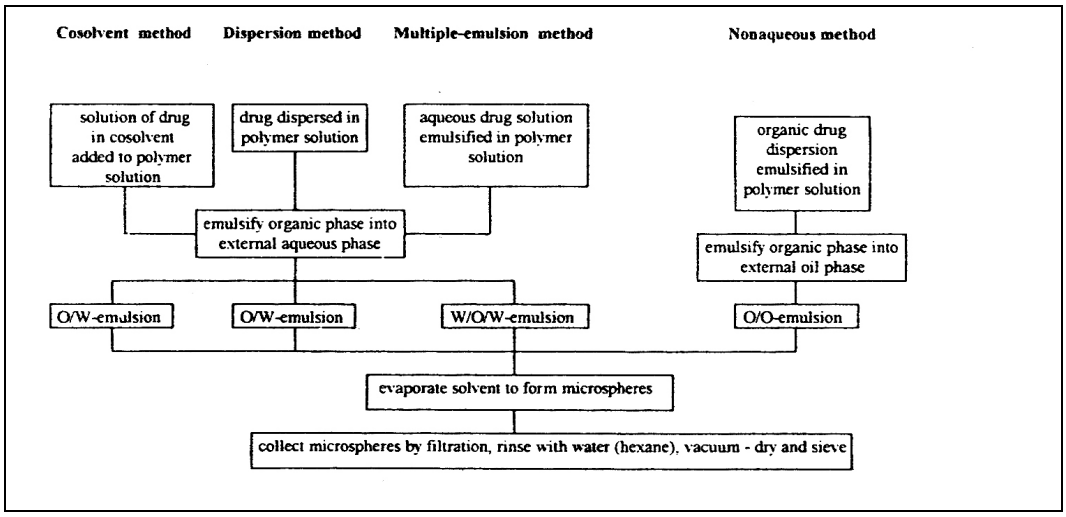
Oil-in-Oil (some times referred as water – in- oil) emulsification process was developed for the encapsulation of highly water- soluble drugs. In this technique, polymer and drug, contained in a polar solvent such as acetonitrile, are emulsified into an immiscible lipophilic phase, with light mineral oil commonly being used, in the presence of an oil-soluble surfactant such as Span.

Table 5 Various formulation factors affecting microencapsulaion process and final product

1	Polymer	Concentration,composition(hydrophilicity/ hydrophobicity,amorphous crystalline),molecular weight, uncapped and capped terminal end group.
2	Drug	Nature and solubility
3.	Solvent	Nature (aqueous and non aqueous)
4.	Emulsifier	Nature and concentration
5.	Emulsification process	Temperature, stirring/ agitation speed, dispersed phase Composition, continuous phase composition, dispersed Phase/ continuous phase ratio.
6	Drug / polyer ratio	
7	Mode of solvent removal	

However an important drawback of using and oil external phase is cleaning up the final product. The oil has to be removed using organic solvents such as n- hexane. Diphenylhydrmine hydrochloride mitomycin C, adriamycin, cephadine and cefadroxin, phenobarbitone and timilol maleate are some examples of drugs that have been encapsulated by this procedure.

Figure 14 Various types of solvent evaporation methods



CONCLUSION

Emulsification/solvent evaporation techniques offer a versatile, easy, and practical method for the manufacturing of biodegradable microspheres. This technique makes possible the entrapment of a wide range drugs having different physical properties and solubility characteristics. It is possible to achieve various drug release profiles by the regulation of copolymer ratio, molecular weight, and size of the microspheres, drug loading, porosity and other formulation parameters.

NON-STEROIDAL ANTI INFLAMMATORY DRUGS

NSAID's [12,13] (A brief review)

In contrast to the opioid analgesics, the non opioid analgesics relieve pain without interacting with the opioid receptors, they posses anti- inflammatory activity and are known as Non-steroidal anti inflammatory drugs (NSAID's). They reduce elevated body temperature and also posses uricosuric property to varying degrees and are non addicting.

Algesia (Pain) : Algesia is an ill defined unpleasant sensation usually evoked by an external or internal noxious stimulus.

Analgesic: A drug that selectively relieves pain without causing loss of consciousness.

MECHANISM OF ACTION

Mainly by inhibiting the biosynthesis and release of prostaglandins. This is done by inhibiting the cyclooxygenase which results in the direct inhibition of the bio synthesis of prostaglandins and thromboxane from arachidonic aicd. There are two forms of cyclooxygenase, COX -1 which is constructive form of the enzyme and COX-2, which is the form induced in the presence of inflammation. These drugs inhibit COX-1 and COX-2 enzymes and hence prostaglandin synthesis. They are chemically classified into many

groups like salicylates, propionic acid derivatives, fenamates, oxicams etc.

NON - STEROIDAL ANTI-INFLAMMATORY DRUGS ARE MAINLY USED FOR

I Colic Pain

II Ectopic Ossification

III Eye disorder (like scleritis)

IV Cystoid Macular Oedema

V Fever

VI Gout

VII Headache

VIII Kidney disorders (Proteinuria)

IX Malignant neoplasm

X Menstrual disorders

XI Migraine

XII Pain

CYCLOXYGENASE ENZYMES (COX -1 & COX-2)

Although the two COX enzymes are similar in their physio chemical properties, they are distinctly regulated at both transcriptional and post transcriptional level.

The introns are much larger in COX-1 genes than in the COX-2 genes, accounting for length of 22- 23 kb and 8-9 kb respectively. The

Cox genes also differ in their promoters and transcripts according for the striking difference in their regulations.

Conventional NSAID's blocks COX -1 by hydrogen bonding to the arginin at 120 positions. At position 523 is an isoleucine molecule in COX-1 and valine in COX -2. The smaller valine molecule in COX-2 leaves a gap in the wall of the channel giving access to side pocket which is thought to the site of binding of many selective COX-2 inhibitors, (often sulfonyl-sulfono sulphonamide groups).

E.g. of COX - 1 inhibitors - Aspirin & Aspirin like compounds

COX - 2 inhibitors- Nimesulide, Meloxicam,

Celecoxib, Rofecoxib

SOLUBILITY-A PREVIEW [14]

Combinational chemistry, Molecular modeling and High throughput Screening have resulted in the discovery of various drug molecules with optimal receptor affinity but of poor biopharmaceutical characteristics. It often results in very hydrophobic compounds with poor solubility which can drastically reduce productivity in drug discovery & development. Drug development is more efficient and robust when compounds are freely soluble. New solubilization technologies will expand the number of New Chemical Entities (NCEs) that can be formulated to meet pharmacochemical thresholds. Advances in particle engineering, encapsulation, surface property optimization and solubility enhancement are enabling the creation of new formulation of both new & existing compounds.

Influence of drug solubilization on business strategies

A drug should be soluble at physiological site to be readily delivered to the cellular membrane while retaining their hydrophobic properties. As growing number of new active compounds exhibit a very low solubility in biological media, the pharma industry is taking a major challenge to find routes to formulate such compounds in order to reach an acceptable bioavailability. Extra time & resources are necessary to develop & test custom formulations for poorly water-soluble compounds. Though a pre-clinical formulation has been successfully

developed, reformulation may be required to obtain a formulation acceptable for clinical studies.

More than one-third of drugs listed in USP are poorly soluble. "Good" or "Bad" solubility depends on the expected dose. For an average potency of 1 mg/kg, "Good" solubility should be at least 0.05g/L and "Bad" solubility should be less than 0.01g/L. The problem of poor solubility might 'be resolved by formulation development, but improvement of solubility by changing the molecule would be a better approach.

Drug solubilization technology

The solubility of drugs can be enhanced by the following approaches

1. Spray drying - Here the solubility of the insoluble drug is enhanced by encapsulating the drug particle with a hydrophilic polymer.
2. Complexation by Cyclodextrins - Cyclodextrins is cyclic oligomers of α-D-glucopyranose. It forms inclusion complexes with a host of compounds.
3. Change in physical property - Solubility of lipophilic compounds is attributed due to this fact.
4. Solubilization using cosolvents
5. Emulsions and microemulsions for drug Solubilization and delivery.
6. Micellization and drug solubility enhancement.

7. Liposomes in Solubilization.
8. Using Pharmaceuticals salts.
9. Prodrugs for improved aqueous solubility.
10. Solid dispersions.
11. Alteration of the solid state of the drug substance.
12. Particle engineering for enhanced bioavailability -Unique nano structured particles with enhanced performance attributes can be obtained through the control of particle size, particle surface area and particle morphology.
13. Supercritical Fluid Processing - Includes Supercritical Fluid extraction, Supercritical Fluid Chromatography, and Supercritical Anti-Solvent processes (SAS). In SAS a substance dissolved in a liquid is precipitated by contacting the solution with a compressed gas in which the substance is sparingly soluble.
14. Porous Microparticles - Microparticles are useful in the delivery of a wide range of drugs. The suitability of microparticles for use in drug delivery depends on a variety of characteristics, including size and porosity. They are used to deliver drugs intravenously so that they can pass safely the blood vessels, for increasing the surface area of a drug so that it will dissolve more rapidly. Porosity is important for entrapping gas in micropraticles, for controlling the release rate of the drug from a microparticle.
15. Starch derivatives and use of pharma grade resins.

LITERATURE REVIEW

- **Ghosh S** [23], et al., studied Diclofenac sodium, a non-selective cyclo-oxygenase inhibitor and etoricoxib, a selective cyclo-oxygenase-2 inhibitor have been widely used in treatment of patients with osteo-arthritis. Five hundred and eighty-five patients with uncomplicated knee osteo-arthritis were randomly allocated into 3 equal groups and received either diclofenac sodium, etoricoxib or placebo in a double-blind manner. The response in both the drug groups was comparable and much more than placebo group. The study shows that etoricoxib provides better clinical efficacy and gastro-intestinal tolerability in osteo-arthritis in comparison to diclofenac sodium presumably due to the selective inhibition of cyclo-oxygenase-2 by etoricoxib.
- **Patel HM**, [24] et al., studied the binary system of etoricoxib with beta-cyclodextrin (beta-CD) was prepared by the kneading method. Drug-cyclodextrin interactions in solution were investigated by the phase solubility analysis. Differential scanning calorimetry, infrared spectroscopy, powder X-ray diffractometry and microscopic study were used to characterize the solid state of all binary systems, whereas their dissolution properties were evaluated according to the USP XXIII paddle method. The results indicate partial interaction of the drug with beta-CD in the physical mixture and complete interaction in the kneaded complex. The dissolution of etoricoxib was notably increased as compared to pure drug as well as its physical mixture. The complex showed more than 75% drug released in 30 min.
- **Chauhan B**, [25] et al., prepared and characterizes solid dispersions of poorly water-soluble drug etoricoxib using lipid carriers by spray drying technique. The absence of etoricoxib peaks in XRPD profiles of solid dispersions

suggests the transformation of crystalline etoricoxib into an amorphous form The in-vitro dissolution test showed a significant increase in the dissolution rate of solid dispersions as compared with pure etoricoxib, spray-dried etoricoxib, and physical mixtures of drug with lipid carriers. Therefore, the dissolution rate of poorly water-soluble drug etoricoxib can be significantly enhanced by the preparation of solid dispersions using lipid carriers by spray drying technique.

- **Zhou HY**, [26]et al., used Ranitidine hydrochloride, as a model drug has done Water in oil in water (W/O/W) emulsion and solvent evaporation methods were used to make chitosan/ cellulose acetate (CCA) microspheres sized 200 - 400 microm. The loading efficiency and release rate of ranitidine were affected by chitosan concentration and molecular weight. Microspheres smaller than 280 microm released the drug faster than did the bigger by about 10%. The optimal condition for the preparation of the microspheres was chitosan concentration 2%, molecular weight 1130 KD. The ranitidine release from the microspheres was 30% during 48 h in phosphate-buffer saline medium.
- **Fundueanu G,** [27] et al., worked about the transport bioadhesive microspheres loaded with DNA to intestine and to test their bioadhesive properties. Poly(vinyl alcohol) (PVA) microspheres were prepared by dispersion reticulation with glutaraldehyde and further aminated. These microspheres were firstly loaded with

plasmid DNA by electrostatic interactions and then entrapped in cellulose acetate butyrate (CAB) microcapsules for gastric protection. The entrapped PVA microspheres do not have enough force by swelling to produce the rupture of CAB shell, therefore the resistance of microcapsules was weakened by incorporating different amount of the pH/thermosensitive polymer (SP) based on poly(N-isopropylacrylamide-co-methyl methacrylate-co-methacrylic acid) (NIPAAm-co-MM-co-MA). This polymer is insoluble in gastric juice at pH 1.2 and 37 degrees C, but quickly solubilized in intestinal fluids (pH 6.8 and pH 7.4). Therefore, DNA loaded PVA microspheres were not expelled in acidic media but were almost entirely discharged in small intestine or colon. The integrity of DNA after entrapment was tested by agarose gel electrophoresis indicating that no DNA degradation occurs during encapsulation. In conclusion DNA loaded microspheres were progressively discharged in intestine. The integrity of DNA was not modified after entrapment and release, as proved by agarose gel electrophoresis. Both loaded and un-loaded aminated microspheres display good bioadhesive properties.

- **Constantin M,** [28] et al., prepared Poly(vinyl alcohol) (PVA) microspheres by dispersion reticulation with glutaraldehyde and further aminated. These

microspheres were firstly loaded with diclofenac (DF) and then entrapped in cellulose acetate butyrate (CAB) microcapsules by an o/w solvent evaporation technique for intestinal delivery of drug. The encapsulated PVA microspheres due to their low swelling degree in intestinal fluids, do not have enough force to produce the disruption of CAB shell, therefore different amounts of succinoylated pullulan microspheres (SP-Ms) (exchange capacity up to 5.2 meq/g) were co-encapsulated. The SP-Ms do not swell in acidic pH, but swell up to 20-times in intestinal fluids causing the rupture of CAB shell and facilitating the escape of loaded PVA microspheres.

- **Varshosaz J,** [29] et al., developed a colon specific drug delivery system for Mezalazine (5-ASA) cyclo-oxygenase inhibitor and anti-inflammatory drug effective in Crohn's disease and ulcerative-colitis which is rapidly absorbed from Intestine. Coated chitosan microspheres were used for this purpose by an emulsion-solvent evaporation technique based on a multiple w/o/w emulsion. Four hundred milligrams of chitosan solution (3%) in dilute acetic acid (0.5 M) containing 12% 5-ASA was dispersed into 2 ml solution of cellulose acetate butyrate (CAB) in methylene chloride. The primary induced w/o emulsion was dispersed into a 1% PVA aqueous solution to produce a w/o/w multiple emulsion. From the dissolution studies microspheres of chitosan with medium Mw and 1 : 1 core/coat that showed the

greatest release of drug (near 80%) in the presence of caecal secretions with a zero-order mechanism

- **Yang D**, [30] et al., were prepared ,Oxidized cellulose acetate alkyl esters (OCAM, OCAOCT, and OCACET) by reacting oxidized cellulose acetate (OCA) with methanol, octanol, and cetyl alcohol, respectively, using dicyclohexylcarbodiimide (DCC) and 4,4'- dimethylaminopyridine (DMAP) as catalysts. OCA alkyl ester microspheres containing 5-FU were prepared by the emulsion-solvent evaporation method using CH2Cl2 as a solvent and polyvinyl alcohol as an emulsifier. Microspheres were characterized by scanning electron and confocal microscopies and powder X-ray diffractometry. Dissolution studies were performed in pH 7.4 phosphate buffer-saline (PBS) at 37 ºC. The analysis of 5-FU was performed spectrophotometrically by measuring absorbance at 286 nm. the new oxidized cellulose esters can be used to prepare biodegradable sustained-release microsphere formulations of 5-FU. The release rate of the drug can be modified by changing the carbon chain length of the alkyl group.
- **Anand Kumar Srivastava,**[31] et al., studied preparation and evaluation of floating microspheres with cimetidine as model drug for prolongation of gastric residence time. The

microspheres were prepared by the solvent evaporation method using polymers hydroxypropylmethyl cellulose and ethyl cellulose. The shape and surface morphology of prepared microspheres were characterized by optical and scanning electron microscopy, respectively. In-vitro drug release studies were performed and drug release kinetics was evaluated using the linear regression method. The prepared microspheres exhibited prolonged drug release (-8 h) and remained buoyant for > 10 h. In-vitro studies demonstrated diffusion-controlled drug release from the microspheres.

- **Adi I,** [32] et al., prepared Ibuprofen Microsperes using using cellulose acetate by emulsion-solvent evaporation method using Polyethylene glycol was used as a surfactant at the ratio of 1:2:1 for drug:polymer:PEG. The microspheres were prepared at three different speeds speeds (800, 1200, 1600 rpm), and were subjected to stability studies for 3 months . The particles decreased with increasing stirrer speed. The physical properties and release profiles of ibuprofen microspheres did not change after storage under accelerated stability conditions for 3 months.
- **Palmieri G F**,[33] et al., utilized polymers for gastroresistant film coating of tablets or pellets such as cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP), and Eudragit L and S

were used in the preparation of drug/polymer matrix tablets. These tablets were prepared either by direct compression of both powders or by the formulation of microspheres that were then compressed. The microspheres were characterized by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and X-ray diffractometry analyses. Dissolution studies were finally carried out to verify if the tablets possessed gastroresistant or controlled-release characteristics. Except for Eudragit L, the polymers can be used under certain conditions in the formulation of modified-release tablets.

- **Soppimath K S**,[34] et al., prepared microspheres loaded with two antihypertensive drugs viz., nifedipine (NFD) and verapamil hydrochloride (VRP) using cellulose-based polymers viz., ethyl cellulose (EC) and cellulose acetate (CA). The microspheres were characterized for their particle size and distribution, tapped density and encapsulation efficiency. Smaller sized particles with a narrow size distribution were produced with EC when compared to CA matrices. The microspheres were directly compressed into tablets using different excipients. The drug release from CA was faster than EC microspheres and, also, the VRP release was faster than NFD

- **Bhardwaj S B**,[35] et al., were prepared microspheres of verapamil hydrochloride, with three different cellulose esters namely cellulose acetate (CA), cellulose acetate propionate (CAP) and cellulose acetate butyrate (CAB) by emulsion-solvent evaporation method. Drug release from the microspheres was affected by the nature of polymer. Mathematical modelling of drug release data by fitting the data to various equations

revealed that the data did not fit the conventional Higuchi's and aker-Lonsdale's models for drug release from spherical matrices. Instead, the data fitted the log-probability and the Weibull models quite well

- **Rodríguez M**,[36] et al., studied a multiparticulate dosage form consisting of a hydrophobic core coated with a pH-dependent polymer is proposed for colonic specific delivery of drugs. Different approaches for olon-specific drug delivery have been studied over the last decade, including prodrugs, polymeric coating using pH-sensitive or bacterial degradable polymers and matrices. In this work, we present a new multiparticulate system to deliver active molecules to the colonic region, which combines pH-dependent and controlled drug release properties. This system was constituted by drug loaded cellulose acetate butyrate (CAB) microspheres coated by an enteric polymer (Eudragit(R) S). Both, CAB cores and pH-sensitive microcapsules, were prepared by the emulsion-solvent evaporation technique in an oily phase. The in-vitro drug release studies of pH-sensitive microcapsules containing the hydrophobic cores showed that no drug was released below pH 7.
- **Goto S,** [37] et al., reported that microencapsulation of ketoprofen using Eudragit E, L and S (acrylic resins) was investigated. The preparation is based on the dispersion of acetone containing ketoprofen in liquid paraffin. Aluminium tristearate was used as an additive for the preparation of microcapsules. In the preparation of microcapsules, the reproducibility of the Eudragit E microcapsule was better than that of Eudragit L and S microcapsules. The microcapsules obtained were uniform and free-flowing particles. From the phase diagram of ketoprofen-Eudragit E or S-aluminium tristearate, it

became clear that the region in which the spherical microcapsules ranging from 250 to 1000 microns in size could be prepared was limited. The dissolution patterns of ketoprofen from Eudragit E, L and S microcapsules were dependent on the pH of the dissolution medium.

- **Palmieri GF**, [38] et al., were prepared ketoprofen gastroresistant microspheres by spray-drying using common pH dependent polymers, such as Eudragit S and L, CAP, CAT and HPMCP. The long ketoprofen recrystallization time was a serious hindrance to the preparation of microspheres having a drug content higher than 35%.Acrylic polymers (Eudragit L or S) are considerably more effective than the cellulosic derivatives CAP and CAT, while the HPMCP profile is in an intermediate position. In HCl 0.1 N, the percentage of ketoprofen released from the tablets is always close to zero, independently from the polymer used.
- **Brahma N,** [39] et al., studied the potential interactions among a model drug (azathioprine; AZA), polymers and a divalent metal ion, which were utilized in the development of a novel multiparticulate formulation for colonic delivery. The approach involved preparation of beads by ionotropic gelation of deacylated gellan gum (DGG) in the presence of Ca^{2+} ions, followed by coating with Eudragit®S-100
- **Kim B K**,[40] et al., prepared microspheres containing the anti-hypertensive drug, felodipine, by the emulsion solvent evaporation method (o/o) using acrylate methacrylate copolymers, Eudragit RL PO and Eudragit RS PO, as wall materials. The release profiles and encapsulation efficiencies depended strongly on the structure of the polymers used as wall materials. The release rate of the Eudragit RS PO microspheres was much lower than that of Eudragit RL PO microspheres. Whereas Eudragit RL PO microspheres

followed the Higuchi rule, Eudragit RS PO microspheres exhibited a triphasic release profile. It is concluded that drug release rate can be controlled by choice of polymer type.

- **Krishnamachari Y**, [41] et al., prepared a microparticulate system consisting of non-enzymatically degrading poly(dl-lactide-co-glycolide) (PLGA) core and delivering budesonide site specifically to distal ileum and colon was developed. Budesonide-loaded microparticles were fabricated using solvent evaporation technique and formulation variables studied included different molecular weight grades of PLGA polymer as well as concentration of polymer, surfactant and drug. Eudragit S-100, an enteric polymer, was then used to form a coating on the surface of budesonide-loaded PLGA microparticles for site specific delivery to the distal ileum and colon. The budesonide-loaded PLGA microparticles coated with Eudragit S-100 coating showed a decrease in entrapment efficiency with an accelerated in-vitro drug release. Moreover, complete retardation of drug release in an acidic pH, and, once the coating layer of enteric polymer was dissolved at higher pH (7.4 and 6.8), a controlled release of the drug from the microparticles were observed. From the results of this investigation, the application of double microencapsulation technique employing PLGA matrix and Eudragit S-100 coating shows promise for site specific and controlled delivery of budesonide in Crohn's disease.
- **Obeidat W M**, [42] et al., investigated Microencapsulation of the anti-inflammatory drug piroxicam and the anti-asthmatic drug theophylline as a means of controlling drug release and minimizing or eliminating local side effects. Microspheres of both drugs that are different in the chemical nature and size were successfully encapsulated at a theoretical loading of 25% with the pH

sensitive Eudragit S 100 polymer using the emulsion-solvent evaporation method. Both preparations exhibited an initial rapid release in the acidic medium with theophylline showing a larger increase in the amount released during this stage. The drug release was sustained for both preparations at pH 6.5 with theophylline microspheres, showing more extended release. Drug release rate kinetics followed a Higuchi spherical matrix model for both microsphere preparations.

- **Ali J**, [43] et al., developed microspheres for celecoxib to enhance its bioavailability by increasing its gastric residence time. Four different polymers-polyethylene oxide, Eudragit S, cellulose acetate, and Eudragit RL-were used to form the floating microspheres using an emulsion-solvent diffusion technique. Microspheres prepared with polyethylene oxide:Eudragit S:celecoxib (2:2:1) gave the best in-vitro percentage release and was taken as the optimized formulation. By fitting the data into zero order, first order, and Higuchi model, it could be concluded that the release followed first-order release kinetics. The correlation coefficient (R2 value) was obtained upon fitting the data to Higuchi equation, which signifies that the mechanism of release of celecoxib from the microspheres was diffusion rate-limited.
- **Mura P**,[44] et al., developed a new colonic drug delivery system which takes advantage of the combined approaches of a specifically colon-biodegradable pectin matrix with a pH-sensitive Eudragit S100 polymeric coating. The developed system was able to suitably retard the onset of drug release and to provide a colon-specific delivery, thus overcoming the problems of pectin solubility in the upper gastrointestinal tract and low site-specificity of simple pH-dependent systems the importance of using appropriate dissolution test conditions to adequately characterize the drug release profiles from delivery

systems endowed with a microflora-activated drug release triggering mechanism has been demonstrated.

- **Shimpi S**, [45] et al., evaluated the ability of polyglycolized glycerides (Gelucire) in protection of amorphous form of drug during compression and shelf life with lower proportion. Amorphous etoricoxib (AET) was prepared by spray drying technique. Tablets of AET and melt granules of AET (MG-AET) with Gelucire 50/13 were prepared. Spray drying yielded the amorphous etoricoxib. Content uniformity in the tablet was in between 95 to 105%. Other parameters like disintegration and hardness were well within the limits. The results showed significant difference in the degree of crystallinity between AET tablet and MG-AET tablet. MG-AET tablet showed absence of crystallinity after 3 months storage. The reason could be formation of hydrogen bonding between the Gelucire and AET. Gelucire yielded a soft embedding during tableting, which prevented the polymorphic transformation. Polyglycolized glycerides are able to protect amorphous etoricoxib during compression with less amount .

SCOPE AND PLAN OF WORK

Research, development and sale of drug delivery system are at a rapid place throughout the world. This world guide trend will intensify in the next decades as cut in public health expenses demand lower cost and efficiency. To meet this demand, many efficient drugs currently in use will be reformulated with delivery systems that can be value added for optimal molecular activity.

The main objective of any drug therapy is to achieve a drug therapy in the desired concentration of the drug in blood or tissue which is therapeutically effective and non-toxic for an extended period of time. Controlled release technology has rapidly emerged over the past three decades as a new interdisciplinary science that offers novel approaches to micro particulate dosage form for bioactive agent. So far natural and synthetic polymers were employed to attain control over release pattern of the drug, unlike synthetic polymers, natural polymers which are polysaccharides have the advantage to better bio compatibility and non-toxicity. Microencapsulation is a technique that can be used to formulate a sustained release system for a drug.

Colon - specific delivery can be achieved with as suitable mechanism that triggers off the drug release upon reaching the colon. The physiological changes in the pH of the gastrointestinal tract have

been extensively exploited to convey the actives to the colon. Method based on pH sensitive delivery, such as delayed - onset dosage forms, could be a simple and practical means for colon targeting. The pH sensitive systems prevent drug release in stomach, whereas releases the contents in intestine and thus causes a delayed release. The polymers should withstand the acidic pH of stomach and proximal part of small bowel and selectively disintegrate in intestinal pH, preferably in ileocecal junction.

Polymers like Eudragit SO, Eudragit LO, and Eudragit S 100 etc. are used which are soluble at pH values higher than 7. The pH of the colon of the normal subjects drops from 7.5 ± 0.4 in the terminal ileum to 6.4 ± 0.6 in the ascending colon. To avoid the release of drug in the terminal ileum rather than in colon is by using two polymers i.e. pH sensitive and also other imparting a controlled release property. Eudragit S was used to prevent the drug release till the formulation reaches the terminal ileum, whereas cellulose acetate avoided the complete release in the ileum and effectively conveys the drug to the colon.

The drug used in the study was Etoricoxib, which is Cycloxygenese- II inhibitor. The daily dose of etoricoxib is 60 mg to 120 mg the drug satisfies all the criteria needed for a drug to be formulated into

sustained release system. In the study the method adopted for micro encapsulation was solvent evaporation technique.

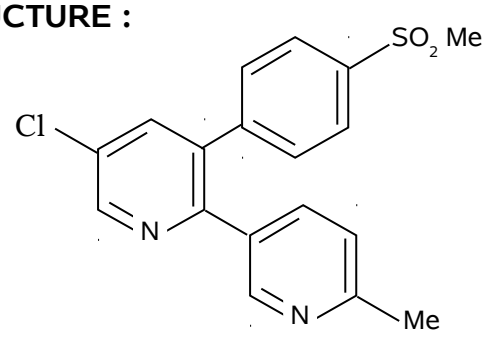
The work has been planned in 5 stages namely

1. Development of calibration curve
2. Compatibility evaluation between drug and carrier.
3. Preparation of cores with cellulose acetates containing the drug.
4. Coating of the prepared cores with the polymer Eudragit S 100.
5. In-vitro dissolution studies.

Drug Profile

ETORICOXIB [46, 47]

1. **STRUCTURE :**



2. **CHEMICAL NAME** : 5- CHLORO-2-[6-METHYL PYRIN -3-Y]-3-[4-METHYL SULFONYL PHENYL]PYRIDINE

3. **PHARMACOLOGICAL CLASSIFICATION** : CYCLOOXYGENASE II INHIBITOR

4. **THERAPEUTIC CLASSIFICATION** OSTEOARTHRITIS,RHEUMATOID ARTHRITIS

5. **PROPERTIES:** Off white crystalline powder , relatively insoluble in water and freely soluble in alkaline aqueous solutions

6. **MECHANISM OF ACTION** :

Etoricoxib is a non steroidal anti-inflammatory agent (dipyridinyl derivative) for oral administration. It is a selective inhibitor of cyclooxygenase-2 (COX-2) i.e. by the direct inhibition of the bio synthesis of prostaglandins and thromboxane from arachidonic acid.

7. INDICATIONS AND DOSAGE

7.1 Dental Pain : Single oral doses of 120mg have been effective

Adult: single oral doses of 120mg have been effective in treatment of acute pain following dental surgery pain relief was not greater with doses of 180 or 240 mg. In these studies, duration of action of at least 24 hours was reported with 120-mg doses.

7.2 Dysmenorrhea

Adult: Etoricoxib was more effective than placebo and as effective as naproxen sodium for relieving pain of dysmenorrhea.

7.3 Osteoarthritis: Once daily doses of 30mg or 60mg have shown efficacy in patients with osteoarthritis of the knee. The 60 mg dose tended to be more effective than 30mg

7.4 Rheumatoid Arthritis : Oral etoricoxib 90 or 120 mg once daily was effective in treating rheumatoid arthritis

8. ADULT DOSAGE

Normal Dosage

Oral route

1) Optimal doses have not been clearly established in any indication.

2) An oral dose of 120 mg has been effective in acute DENTAL PAIN; no additional benefit was seen with higher doses (180 or 240 mg)

3) In RHEUMATOID ARTHRITIS, 90 or 120 mg once daily has been effective

4) Once-daily doses of 30 or 60 mg have shown efficacy in patients with OSTEOARTHRITIS of the knee. The 60 mg dose tended to be more effective than 30 mg; efficacy was similar with 60 and 90 mg once daily

9 PHARMACOKINETICS

9.1 ADME

9.1.1 Absorption

A) Bioavailability

1) ORAL, TABLET: 80% to 100%

a) In one study, the pharmacokinetics of etoricoxib appeared similar with use of four different tablet formulations.

b) Antacids (calcium carbonate, aluminum/magnesium hydroxide) do not significantly affect the absorption of etoricoxib

B) Effects of Food

1) Decreased rate of absorption but no effect on extent of absorption

a) A 120mg dose administered after a high-fat meal resulted in 36% lower C_{max} and a 2-hour delay in t_{max}, but no change in AUC

9.2 Distribution

A) Distribution Kinetics

1) Volume of Distribution: 119 L at steady state following 24mg single intravenous dose

9.3 Metabolism

A) Metabolism Sites and Kinetics

1) LIVER, at least 90%

a) The major metabolic pathway is 6'-methyl hydroxylation, primarily via cytochrome P450 (CYP)-3A4. Other metabolites include the 1'-N-oxide, 6'-carboxylic acid, and 6'-hydroxylated glucuronide.

9.4 Excretion

A) Kidney 1) Etoricoxib is excreted in the urine, primarily as metabolites.

B) Other

1) OTHER EXCRETION

a) TOTAL BODY CLEARANCE: 0.049 L/minute following 25mg single intravenous dose

b) FEACES: Etoricoxib is excreted in the feces, primarily as metabolites.

10 CONTRAINDICATIONS AND PRECAUTIONS

10.1 Contraindications

A) Previous hypersensitivity to etoricoxib

B) Acute peptic ulcer disease or GI bleeding

C) Patients with a history of bronchospasm with rhinoconjunctivitis or urticaria/angioedema associated with aspirin or other nonsteroidal anti inflammatory agents (adult-onset asthma, chronic rhinitis, nasal polyps, and chronic urticaria/angioedema predispose to these reactions) (risk of anaphylactic-like reactions)

D) Severe renal or hepatic disease

10.2 Precautions

A) History of mild allergic phenomena related to ingestion of other non steroidal anti inflammatory drugs (e.g., rash)

B) Conditions predisposing to gastrointestinal events (e.g., history of peptic ulcer, upper gastrointestinal disease, ulcerative colitis; smoking; advancing age,concurrent aspirin or corticosteroids; alcohol abuse; stress)

C) Patients with hypertension, recent MI, angina, or other cardiovascular disease

D) Patients with bleeding disorders (potential exacerbation)

E) Mild or moderate liver disease (pharmacokinetic data lacking; enhanced risk of adverse events, such as fluid retention)

F) Mild or moderate renal impairment (pharmacokinetic data lacking; potential for adverse renal effects, particularly in the elderly); there is no convincing evidence that COX-2 selectivity reduces the risk of renal toxicity relative to nonselective agents

G) Patients with risk factors for renal failure (e.g., diabetes, preexisting edema, hypovolemia, sepsis); there is no convincing evidence that COX-2 selectivity reduces the risk of renal toxicity relative to nonselective agents

11. ADVERSE DRUG REACTIONS:

11.1 Cardiovascular system

11.1a: Small increase in blood pressure have been reported with doses of 60mg or 90 mg

11.1b: Thromboembolic disorder

11.2 Gastrointestinal

11.2 a Significantly fewer upper gastrointestinal events and uncomplicated GI events with etoricoxib than with diclofenac in patients with osteoarthritis and rheumatoid arthritis.

11.2 b Nausea, vomiting, diarrhea, heart burn, taste disturbances, decreased appetite and flatulence

11.2 c Head ache, dizziness, fatigue and insomnia

12. DRUG INTERACTIONS

Drug –drug Combinations

Cytochrome p 450 , isoenzyme cyp3A4 inhibitors or inducers , rifampicin , ethyloestradiol, oral salbutamol,and minidoxil. Antidepressants SSRIs and Venlaflaxine may increase risk of bleeding .Risk of side effects increased with concomitant use of Aspirin , cyclosporin,ketorolac or other NSAID, lithium ,and methotrexate , coumarin ,phenytoin and sulphonyl ureas .

Table-6

MARKETED FORMULATION

PRODUCT	DOSE	DOSAGE	MANUFACTER
EBOV	60MG	TAB	GLENMARK
	90MG	TAB	GLENMARK
	120MG	TAB	GLENMARK
ETOXIB	60MG	TAB	UNICHEM
	90MG	TAB	UNICHEM
	120MG	TAB	UNICHEM

Polymer Profile

1.CELLULOSE ACETATE [48,49]

1. Non proprietary Names

- BP: Cellulose acetate
- PhEur: Cellulosi acetas
- ESPNF: Celluliose acetate

2. SYNONYMS

Acetyl cellulose;cellulise diacetate;cellulose triacetate.

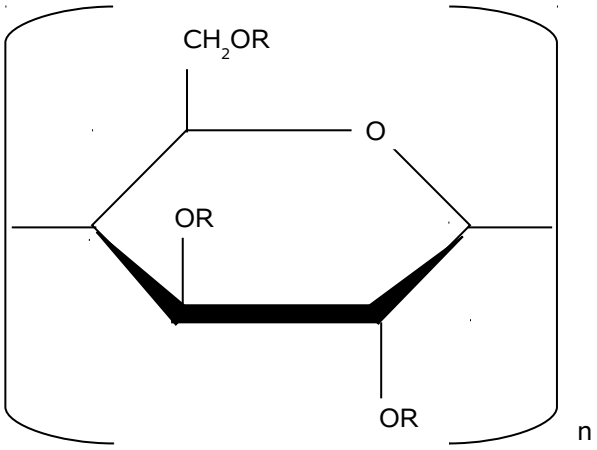
3. CHEMICAL NAME AND CAS REGISTERY NUMBER

- Cellulose acetate (9004-35-7)
- Cellulose diacetate (9035-69-2)
- Cellulose triacetate (9012-09-3)

4. DEFINITION

Cellulose acetate is partly or completely *O*-acetylated cellulose. It contains not less than 29.0 percent and not more than 44.8 percent of acetyl groups (C_2H_3O) calculated with reference to the dried substance. The acetyl contents is not less than 90.0 percent and not more than 110.0 percent of that started on the label, calculated with reference to the dried substance.

5. STRUCTURAL FORMULA



6. FUNCTIONAL CATEGORY

Coating agent; release agent; tablets and capsules diluent.

7. APPLICATION IN PHARMACEUTICAL FORMULATION OR TECHNOLOGY

Cellulose acetate is widely used in pharmaceutical formulations both in sustained – release applications and for taste masking.

Cellulose acetate is used as a semi permeable coating on tablets, especially on osmotic pump- type tablets and implants, this allows for controlled, extended release of activity. Cellulose acetate films in conjunction with other materials, also offer sustained release without the necessity of drilling a hole in the coating as is typical with osmotic pump systems. Cellulose acetate and other cellulose esters have also been used to form drug- loaded microparticles with controlled – release characteristics.

Cellulose acetate films are used in transdermal drug delivery systems and also as film coating on tablets or granules for taste masking. For. e.g., acetaminophen granules have been coated with a cellulose acetate- based coating before being processed to provide chewable tablets. Extended- release tablets can also be formulated with cellulose acetate as a directly comprisable matrix former. The release profile can be modified by changing the ratio of active to cellulose acetate and by incorporation of plasticizer, but was shown to insensitive to cellulose acetate molecular weight and particle size distribution.

8. DESCRIPTION

Cellulose acetate occurs as a white to off- white powder, free flowing pellets, or flakes. It is tasteless and odorless, or may have a slight odor of acetic acid.

Figure 15 Scanning electron microscopy of cellulose acetate

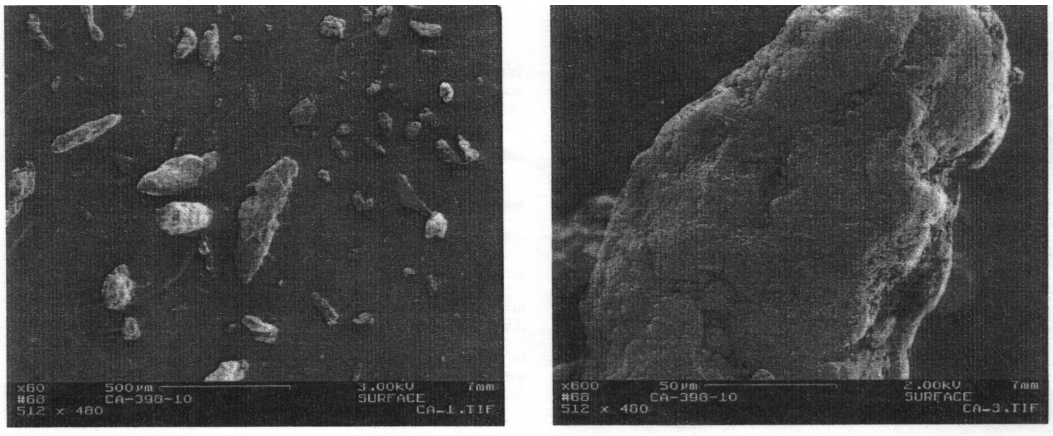


Fig 15(a) **Fig 15(b)**

Fig 15(a) SEM:1

Excipient : Cellulose acetate,CA-398-10 NF

Manufacturer : Eastman Chemical Co.

Lot No. : AC65280NF

Magnification : 60x

Voltage : 3kV

Fig 15(b) SEM 2

Excipient : Cellulose acetate, CA-398-10NF

Manufacturer: Eastman Chemical Co.

Lot No : AC65280NF

Magnification: 600 x

Voltage : 2kV

9. PHARMACOPEIAL SPECIFICATIONS

Table 7 Pharmacopeial specifications

Test	PhEur 2002	USPNF 20
Identification	+	+
Characters	+	-
Loss of drying	≤ 5.0%	≤ 5.0%
Residue on ignition	≤ 0.1%	≤ 0.1%
Free acid	+	≤ 0.1%
Heavy metals	≤ 10ppm	≤ 0.001%
Micorbial contamination	1000/g	-
Organic volatile impurities	-	+
Assay (of acetyl groups)	29.0- 44.8%	29.0-44.8%

10. IDENTIFICATION Prepare a 1 in 10 solution of Cellulose Acetate, previously dried in dioxane. Spread one drop of solution on a sodium chloride plate, place a second sodium chloride plate over it, and spread the specimen between the plates. Separate the plates heat them both at 105˚ for 1 hour and resemble the dried plate; the IR absorption spectrum exhibits maxima only at the same wavelengths as that of a similar preparation of USP Cellulose Acetate RS, treated in the same manner.

11. TYPICAL PROPERTIES

Density (bulk) : typically 0.4g/ cm^3 for powders.

Glass transition temperature : 1700-190˚C

Melting point : Melting range 230-300 ˚C

Solubility : The solubility of cellulose acetate is greatly influenced by the level of acetyl groups present. In general, cellulose acetates are soluble in acetone- water blend of varying ratios, dichloromethane- ethanol blends, dimethyl formamide, and dioxane. The cellulose acetates of higher acetyl level are generally more limited in solvent choice than are the lower-acetyl materials.

Viscosity (dynamic) : Various grades of cellulose acetate are commercially available that differ in their acetyl content and degree of polymerization. They can be used to produce 10% w/v solutions in organic solvents with viscosities of 10-230 mPa s. Blends of cellulose acetates may also be prepared with intermediate viscosity values.

12. STABILITY AND STORAGE CONDITIONS

Cellulose acetate is stable if stored in a well-closed container in a cool, dry place. Cellulose acetate hydrolyzes slowly under prolonged adverse conditions such as high temperature and humidity, with a resultant increase in free acid content and odor of acetic acid.

13. ASSAY

A. **For cellulose acetate containing not more than 42.0 percent of acetyl groups.**

To 2.000 g in a 500ml conical flask add 100ml acetone R and 10ml of water R .Close the flask and stir with a magnetic stirrer until dissolution is complete. Add 30.0ml of 1 M sodium hydroxide with constant stirring. Close the flask and stir with a magnetic stirrer for 30 min. Add 100ml of water for 2 min. and cool to room temperature. Titrate with 0.5M sulfuric acid using 0.1ml phenolphthalein solution R as indicator. Carry out a blank titration .Calculate the percentage content of acetyl groups from the expression.

$$\frac{4.305(n_2 - n_1)}{(100-d) \times m}$$

d = loss on drying as a percentage

m = mass of the substance to the examined, in grams,

n_1 = number of milliliters of 0.5 m sulphuric acid used in the test,

n_2 = number of milliliters of 0.5 m sulphuric acid used in the blank titration.

B. For cellulose acetate containing more than 42.0 per cent of acetyl groups.

To 2.000 g in a 500ml conical flask add 30ml of dimethyl sulphoxide R and 100ml of acetone R. Close the flask and stirrer with a magnetic stirrer for 16 h. Add 30 ml of 1M sodium hydroxide with a constant stirring. Close the flask and stir with a magnetic stirrer for 6 min. Add 100ml of water R at 80˚C, washing down the sides of the flask, stir for 2 min, and cool to room temperature. Titrate with 0.5M hydrochloric acid using 0.1ml of phenolphthalein solution R. Add 3.5ml of 0.5M hydrochloric acid in excess, stir for 50min and allow to stand for 30min. Titrate with 0.5M sodium hydroxide until a persistent pink color is obtained, stirring with a magnetic stirrer. Calculate the net number of milli equivalent of sodium hydroxide consumed, taking the mean of two blank titrations in to consideration. Calculate the percentage content of acetyl groups from the expression.

$$\frac{4.305 \times n}{(100-d) \times m}$$

d = loss of drying as a percentage

m = mass of the substance to be examined in grams,

n = net number of milli equivalent of sodium hydroxide

14. INCOMPATIBILITIES

Cellulose acetate is incompatible with strongly acidic or alkaline substances. Cellulose acetate is compatible with the following plasticizers: diethyl phthalate, polyethylene glycol, triacetin, and triethyl citrate

15. METHOD OF MANUFACTURE

Cellulose acetate is prepared from highly purified cellulose by treatment with acid catalysis and acetic anhydride

16. SAFETY

Cellulose acetate is widely used in oral pharmaceutical products and is generally regarded as a nontoxic and nonirritant material.

17. HANDLING PRECAUTIONS

Observe normal precautions appropriate to the circumstances and quantity of material handled. Dust may be irritant to the eyes and eye protection should be worn. Like most organic materials in powder form, these materials are capable of creating dust explosions. Cellulose acetate is combustible.

18. REGULATORY ACCEPTANCE

Included in the FDA Ingredients Guide (oral tablets)

19. RELATED SUBSTANCES

Cellulose acetate Phthalate.

20. COMMENTS

When solutions are being prepared, cellulose acetate should always be added to the solvent, not the reverse. Various grades of cellulose acetate are available with varying physical properties.

PREFORMULATION STUDIES

Before formulation of drug substance into dosage form, it is essentially that it should be chemically and physically characterized. Preformulation studies give the information needed to define the nature of the drug substance and provide a frame work for the drug combination with pharmaceutical excipients in the fabrications of a dosage form.

QUALITATIVE ANALYSIS

1. Compatibility evaluation

One of the requirements for the selection of suitable polymers or carriers for pharmaceuticals formulation is its compatibility. The study was carried out by using as infrared spectrophotometer to find out if there is any possible chemical interaction between drug and polymers at different ratios.

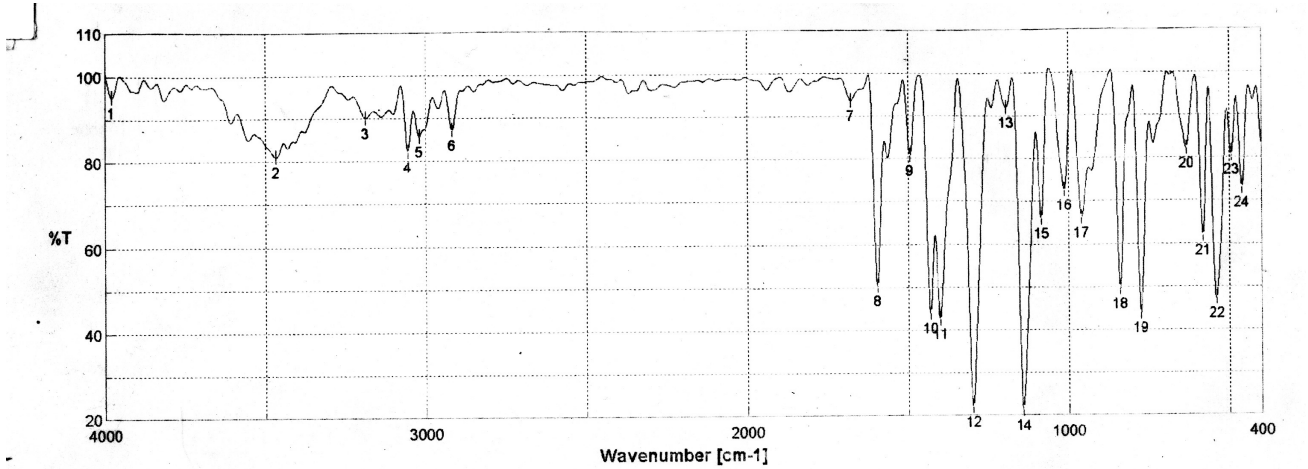
Physical mixture of the drug and the polymer was mixed with 400 mg of potassium bromide. This mixture was compressed to form a transparent pellet in a hydraulic press at 15 tons pressure. The pellet was scanned at 4000 to 400 cm^{-1} in a FT-IR spectrophotometer. Similarly IR spectra of the drug and polymers separately were also recorded. The physical mixture was preserved in air tight containers and the spectra were recorded at 1 and 2 months interval.

IR Spectral Analysis

Using FT-IR 410 PC spectrometer carried out the compatibility studies between drugs and the polymers.

There was no appearance or disappearance of any characteristic peaks, which confirmed the absence of any chemical interaction between drugs and polymer.

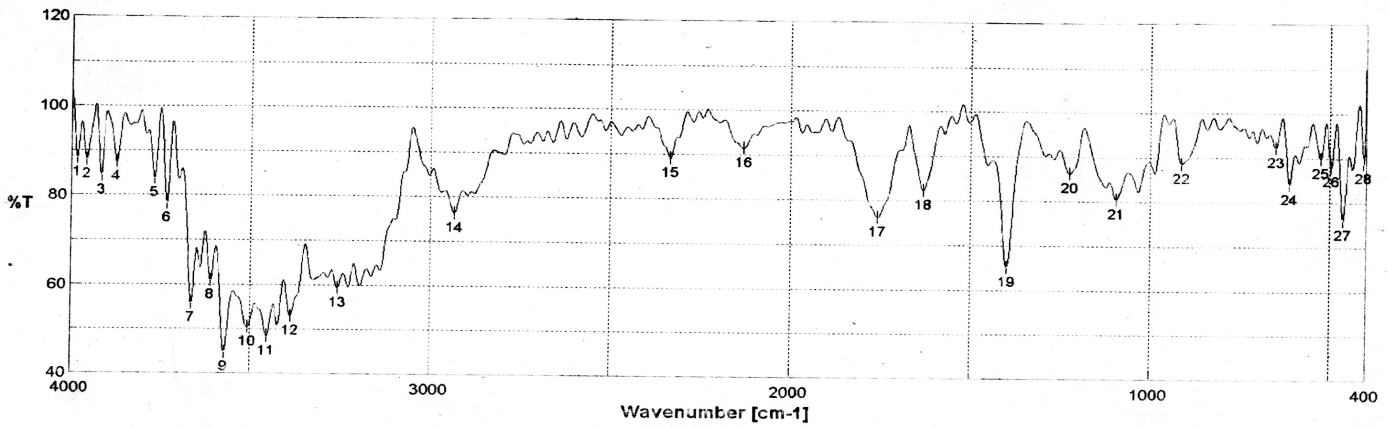
Figure 17 IR Spectra of Etoricoxib



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	4	Scanning Speed	2 mm/sec
Date/Time	12/14/2007 2:42PM	Update	12/15/2007 9:59AM
Operator	C.Geetha		
File Name	A		
Sample Name	A		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3979.39	95.1702	2	3466.42	81.0074	3	3187.76	89.9875	4	3055.66	82.174	5	3020.94	85.7749
6	2918.73	87.2851	7	1677.77	93.7303	8	1596.77	50.4031	9	1494.56	80.7459	10	1430.92	43.979
11	1400.07	42.6843	12	1297.86	22.2147	13	1193.72	92.0485	14	1141.65	21.2623	15	1083.8	66.1529
16	1012.45	72.6341	17	958.448	66.3199	18	839.847	49.651	19	775.244	43.9448	20	635.43	82.2062
21	581.433	61.8443	22	539.971	47.2109	23	493.688	80.7202	24	460.904	73.0639			

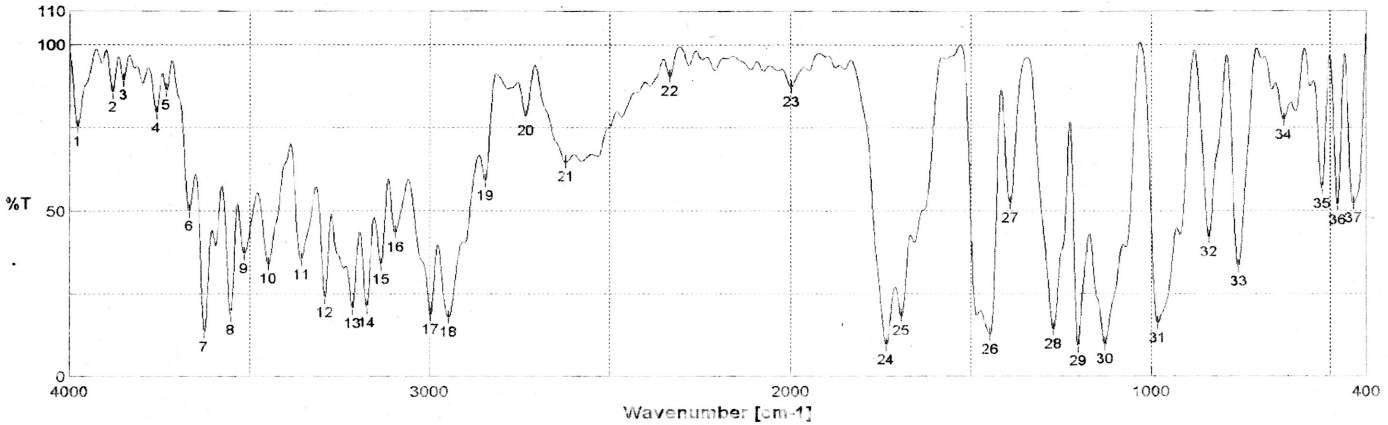
Figure 18 IR Spectra of Cellulose Acetate



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	16	Scanning Speed	2 mm/sec
Date/Time	12/14/2007 4:11PM	Update	12/15/2007 10:01AM
Operator	C.Geetha		
File Name	B		
Sample Name	B		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3984.21	88.3424	2	3958.18	87.9003	3	3916.72	84.2891	4	3873.33	87.4032	5	3767.26	83.7096
6	3732.55	78.0898	7	3664.09	55.7496	8	3611.05	60.9362	9	3571.52	44.925	10	3507.88	50.5208
11	3453.88	48.4216	12	3388.32	52.9469	13	3257.18	59.3335	14	2934.16	76.3637	15	2334.41	89.0805
16	2131.92	91.4405	17	1756.83	76.1881	18	1632.45	82.2624	19	1397.17	55.1549	20	1224.58	86.2876
21	1094.4	80.5744	22	912.165	88.5241	23	650.858	92.2577	24	611.324	83.9731	25	525.507	89.8859
26	495.58	88.1116	27	463.796	76.1035	28	407.871	88.8423						

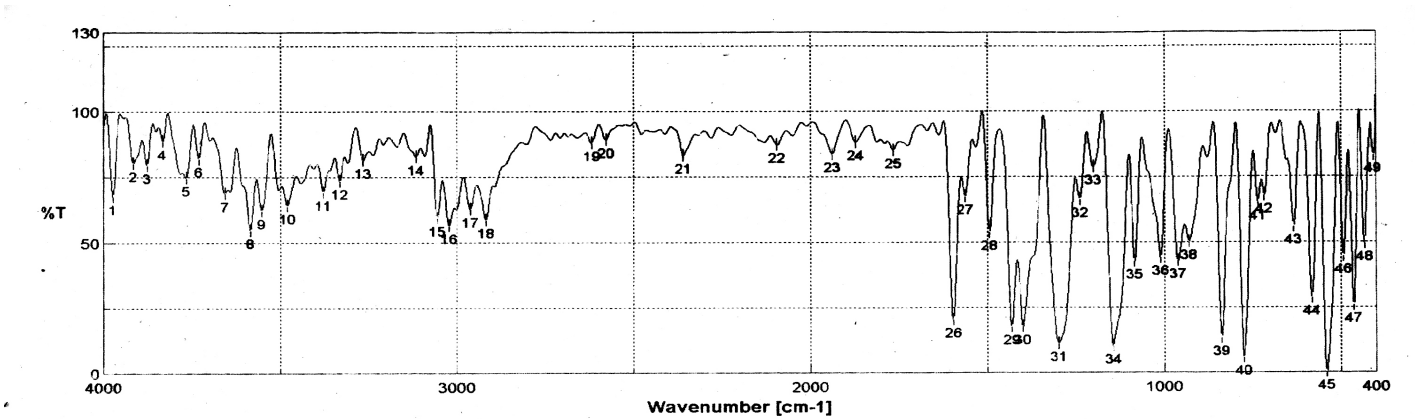
Figure 19 IR Spectra of Eudragit S 100



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	32	Scanning Speed	2 mm/sec
Date/Time	12/14/2007 2:50PM	Update	12/15/2007 10:03AM
Operator	C.Geetha		
File Name	C		
Sample Name	C		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3977.46	75.1828	2	3881.04	85.6724	3	3850.18	89.2978	4	3759.55	79.2993	5	3731.58	86.2711
6	3668.91	49.8635	7	3625.52	13.4454	8	3554.16	18.5865	9	3515.6	37.014	10	3449.06	33.8977
11	3357.46	35.2126	12	3291.99	23.7194	13	3215.72	20.6085	14	3176.19	20.6865	15	3135.69	30.7523
16	3096.15	43.4509	17	2997.8	18.5855	18	2948.63	17.8472	19	2848.35	59.0094	20	2735.53	78.4489
21	2621.75	64.6134	22	2334.41	90.4775	23	1999.82	87.3103	24	1734.66	9.63525	25	1693.19	18.2383
26	1445.39	12.6317	27	1390.42	52.2595	28	1270.86	14.2019	29	1203.36	9.09702	30	1128.15	9.85629
31	981.59	16.1122	32	839.847	42.0259	33	756.923	33.0411	34	630.609	77.2312	35	522.615	56.4821
36	480.188	51.7162	37	435.834	52.1965									

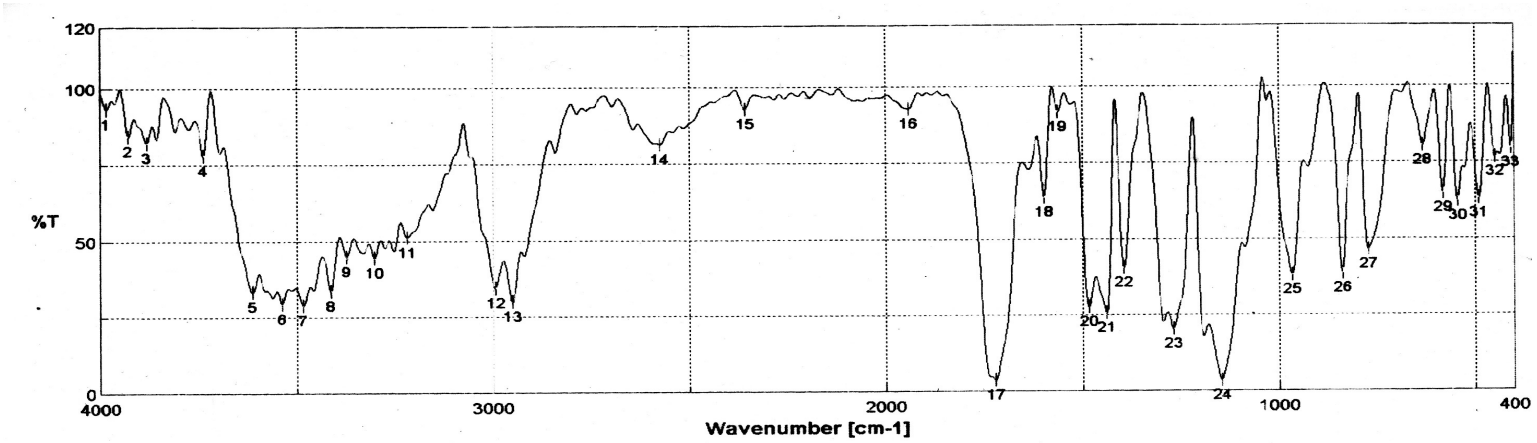
Figure 20 IR Spectra of Etoricoxib and Cellulose Acetate



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	16	Scanning Speed	2 mm/sec
Date/Time	12/14/2007 4:15PM	Update	12/15/2007 10:05AM
Operator	C.Geetha		
File Name	D		
Sample Name	D		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3973.61	67.7436	2	3915.75	80.3594	3	3877.18	79.5202	4	3831.86	88.5745	5	3766.3	74.7394
6	3730.62	82.0185	7	3658.3	68.8625	8	3585.02	54.8163	9	3553.2	62.3516	10	3480.88	64.2606
11	3377.71	69.2603	12	3332.39	73.5662	13	3265.86	81.4525	14	3115.44	82.6236	15	3054.69	59.3052
16	3022.87	56.5025	17	2963.09	62.7997	18	2918.73	58.7236	19	2618.86	87.995	20	2578.36	89.0345
21	2358.52	83.1202	22	2095.28	87.1526	23	1939.07	83.578	24	1872.54	88.0905	25	1767.44	84.9718
26	1596.77	20.4343	27	1563.02	67.404	28	1493.6	53.7597	29	1430.92	17.88	30	1399.1	17.7287
31	1298.82	11.3642	32	1238.08	66.3684	33	1200.47	78.755	34	1143.58	10.36	35	1082.83	42.6656
36	1010.52	44.1743	37	961.341	43.0376	38	930.485	50.2604	39	837.919	13.3801	40	774.279	6.00061
41	734.746	65.1725	42	[illegible]	67.8575	43	633.501	55.9913	44	582.397	28.812	45	539.007	0.558585
46	492.723	44.5841	47	[illegible]	25.9636	48	433.905	49.4853	49	407.871	83.0445			
									54	519.722	78.0239			66.2682

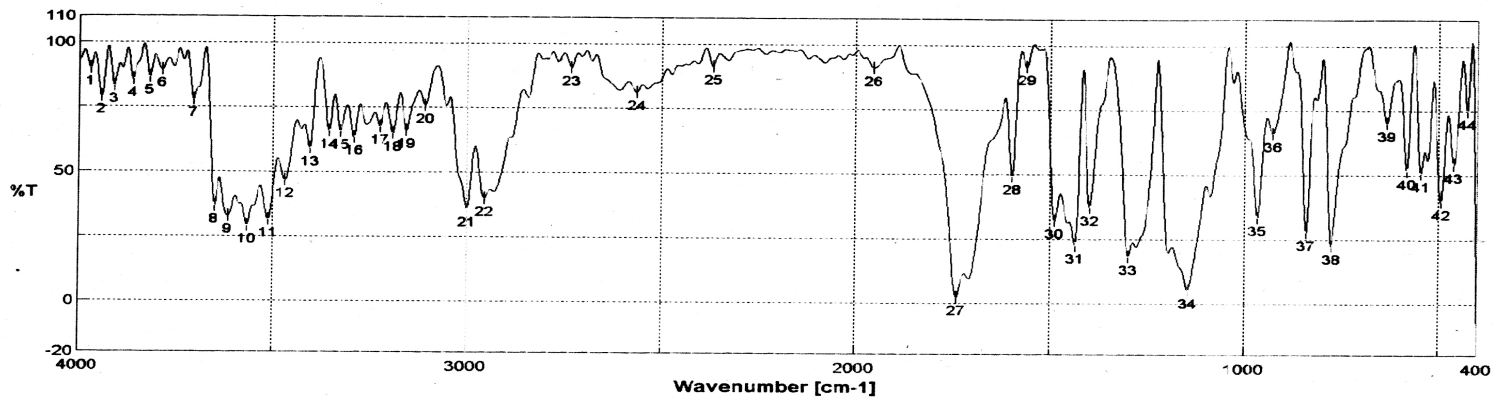
Figure 21 IR Spectra of Etoricoxib and Eudragit S 100



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	16	Scanning Speed	2 mm/sec
Date/Time	12/14/2007 2:55PM	Update	12/15/2007 10:08AM
Operator	C.Geetha		
File Name	E		
Sample Name	E		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3984.21	93.1102	2	3928.29	84.2557	3	3881.04	82.1742	4	3737.37	77.8995	5	3612.98	33.1878
6	3537.77	29.3214	7	3483.78	28.8037	8	3414.35	33.5359	9	3373.85	44.8561	10	3303.46	44.389
11	3219.58	51.1016	12	2994.91	34.476	13	2951.52	29.8618	14	2575.47	81.2735	15	2357.55	92.8056
16	1941	92.7325	17	1722.12	3.69106	18	1598.7	63.6232	19	1562.06	91.6448	20	1483.96	27.6346
21	1438.64	25.6597	22	1394.28	40.5758	23	1269.9	20.3957	24	1145.51	3.48776	25	966.162	38.1261
26	838.883	38.614	27	772.351	46.3409	28	633.501	80.2702	29	582.397	64.8399	30	544.792	62.0544
31	489.831	62.9815	32	449.333	76.4301	33	408.835	79.4339						

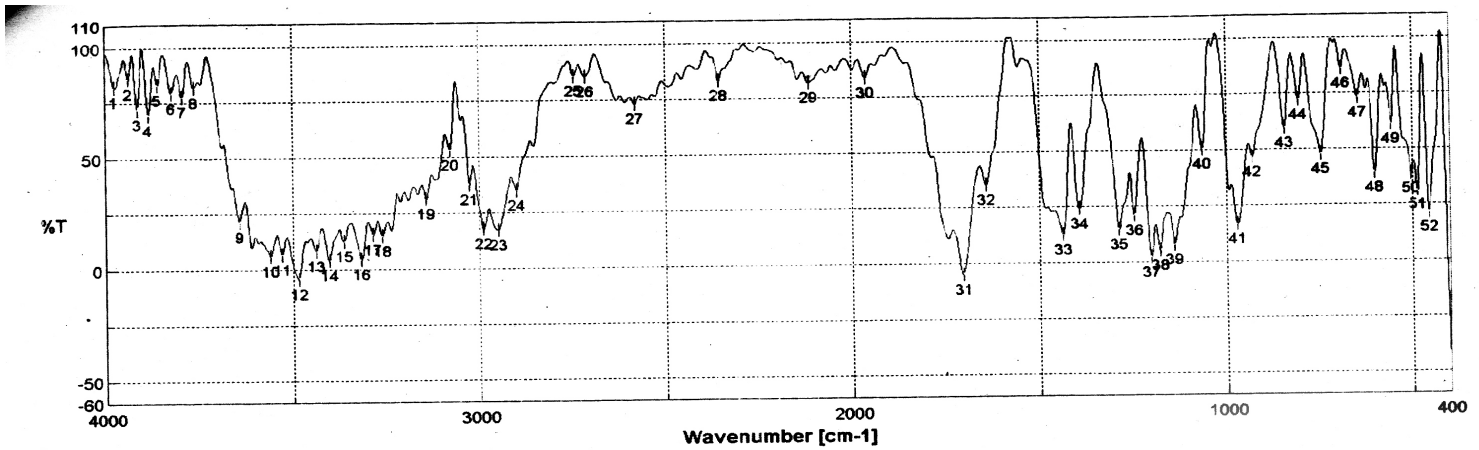
Figure 22 IR Spectra of Etoricoxib,Cellulose Acetate and Eudragit S 100



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	32	Scanning Speed	2 mm/sec
Date/Time	12/14/2007 4:19PM	Update	12/15/2007 10:10AM
Operator	C.Geetha		
File Name	F		
Sample Name	F		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3971.68	89.9232	2	3941.79	78.8969	3	3909	83.0489	4	3861.75	85.3944	5	3818.36	86.4932
6	3786.54	89.3749	7	3705.55	77.8511	8	3649.62	36.8221	9	3615.88	32.806	10	3566.7	29.1365
11	3511.74	31.5283	12	3468.35	46.7226	13	3405.67	59.1128	14	3356.5	65.7636	15	3327.57	65.6463
16	3292.86	63.4809	17	3226.33	67.5665	18	3192.58	64.9377	19	3156.9	65.911	20	3108.69	75.6604
21	3000.69	35.7496	22	2957.3	39.923	23	2732.64	90.5377	24	2565.83	91.2236	25	2368.16	91.2393
26	1954.5	91.0801	27	1740.44	2.38945	28	1597.73	49.2405	29	1561.09	91.7476	30	1487.81	32.1144
31	1435.74	22.5136	32	1398.14	37.1224	33	1297.86	18.2641	34	1143.58	5.34376	35	965.198	33.5169
36	926.628	65.9788	37	839.847	27.7003	38	774.279	22.529	39	634.466	70.0295	40	581.433	51.6863
41	545.756	50.6505	42	493.688	39.7743	43	460.904	54.0144	44	426.191	74.9247			

Figure 23 IR Spectra of Cellulose Acetate and Eudragit S 100



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	32	Scanning Speed	2 mm/sec
Date/Time	12/14/2007 4:26PM	Update	12/15/2007 10:17AM
Operator	C.Geetha		
File Name	G		
Sample Name	G		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3975.53	82.0377	2	3937.93	85.9087	3	3914.79	72.123	4	3884.9	69.3481	5	3859.83	83.0728
6	3824.15	79.2778	7	3794.26	77.6532	8	3763.4	81.7547	9	3642.87	21.3725	10	3559.95	6.01584
11	3529.09	6.76724	12	3485.7	-4.43338	13	3439.42	8.21981	14	3403.74	4.0487	15	3364.21	12.7264
16	3316	4.5362	17	3285.14	15.4568	18	3259.11	14.8615	19	3141.47	31.4064	20	3077.83	53.1158
21	3026.73	37.6049	22	2989.12	17.8138	23	2949.59	17.1481	24	2900.41	34.9557	25	2745.17	85.9298
26	2715.28	85.6354	27	2583.18	73.0924	28	2356.59	83.136	29	2116.49	81.9202	30	1964.14	84.0574
31	1705.73	-4.97934	32	1643.05	35.2725	33	1437.67	12.5968	34	1393.32	24.0946	35	1286.29	14.9327
36	1245.79	21.0755	37	1199.51	2.17148	38	1176.36	5.21023	39	1138.76	7.86189	40	1063.55	50.5697
41	970.019	16.989	42	930.485	46.9167	43	842.74	59.5749	44	805.135	72.3455	45	745.352	47.9016
46	690.391	86.2329	47	646.036	73.0757	48	600.717	39.1692	49	556.363	61.0633	50	503.33	38.6866
51	486.938	31.2858	52	456.082	21.4167									

2. Thin – Layer Chromatography [51]

The preliminary identification of Etoricoxib and also the microspheres was performed by TLC method.

Pre coated TLC plates	:	Manufactured by S.D. Fine Chem. Ltd.
Absorbent layer	:	Silica gel 60 G
Layer thickness	:	0.10 mm
Size	:	10 x 20 cm
Separation Technique	:	Ascending
Mobile phase	:	Chloroform: methanol: Toluene in the ratio 1:2:1:
Chamber saturation	:	The Chamber was lined on three sides and saturated for 30 minutes with the above mobile phase.
Preparation of standard	:	Pure sample of Etoricoxib was dissolved in methanol.
Preparation of Test Sample	:	Sample of drug Etoricoxib was dissolved in methanol
Detection	:	Dark Violet Spot in UV
Rf	:	Distance traveled by the solute spot / Distance traveled by the solvent front

Table 8 Rf values of etoricoxib

Sl.No.	Name of the Sample	Color Detected	Rf Values
1	Standard Drug	Violet	0.606
2.	Test Drug	Violet	0.585

ANALYTICAL METHODS FOR ETORICOXIB

1. High Performance Liquid Chromatographic [53]
2. Reverse Phase High Performance Liquid Chromatographic Method [54]
3. Liquid Chromatography-Tandem Mass Spectrometry with Electro spray Ionization in Human Plasma [55]
4. Liquid Chromatography-Mass Spectrometry Method in Human Plasma [56]
5. High Performance Thin Layer Chromatography [52]
6. UV/Visible Spectrophotometric Method [57]

The present study used UV spectrometric method by using JASCO - UV-530

STANDARD GRAPH OF ETORICOXIB [57]

JASCO-UV-530 spectrophotometer was used for all absorbance measurement .Stock solution of etoricoxib was prepared in methanol.

In the simple UV method aliquots of stock solution of etoricoxib 0.5-2.5ml were transferred into series of 10 ml volumetric flask and the volume was made upto the mark with 0.1N NaOH solution .The absorbance of the resulting solution was measured at 284 nm against the reagent blank (prepared similarly without the drug) .Calibration curve was prepared by plotting concentration Vs absorbance

1. Preparation of Stock Solution

Solution A

100 mg of drug etoricoxib was dissolved in methanol and made up the volume with 100 ml volumetric flask to give 1000µg/ml

Solution B

From this 10 ml was taken and made up the volume with 0.1 N NaOH to give 100 µg/ml.

2. Preparation of Various Concentrations

a. 5 µg/ml Solution ------ 0.5 ml of the stock solution B was made upto volume with 0.1 N NaOH in a 10 ml standard flask

b. 10 µg/ml Solution ------ 1 ml of the stock solution B was made upto volume with 0.1 N NaOH in a 10 ml standard flask

c. 15 µg/ml Solution ------ 1.5 ml of the stock solution B was made upto volume with 0.1 N NaOH in a 10 ml standard flask

d. 20 µg/ml Solution ------ 2 ml of the stock solution B was made upto volume with 0.1 N NaOH in a 10 ml standard flask

e. 25 µg/ml Solution ------ 2.5 ml of the stock solution B was made upto volume with 0.1 N NaOH in a 10 ml standard flask

Procedure:

Various concentrations of etoricoxib in 0.1 N NaOH solution 5-25 µg/ml were prepared as mentioned above .Absorbance of the solution was measured against reagent blank using UV-Visible spectrophotometer. A standard graph was plotted between concentration Vs absorbance. A straight line passing through the origin was obtained .The same procedure was repeated with 0.1 N HCl and mixed phosphate buffer pH 7.5

Table 9 Standard graph of etoricoxib in 0.1 N HCl

Sl.No	Concentration in µg/ml	Absorbance at 284 nm
0	0	0.000
1	5	0.1910
2	10	0.3889
3	15	0.5901
4	20	0.7862
5	25	0.9881

Figure 24 Standard graph of etoricoxib in 0.1 N HCl

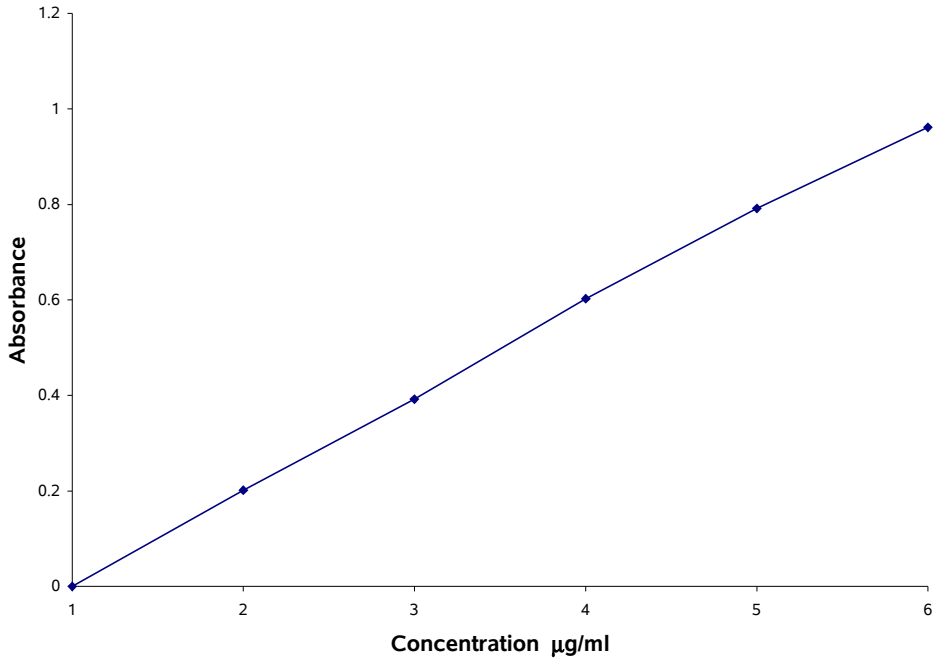
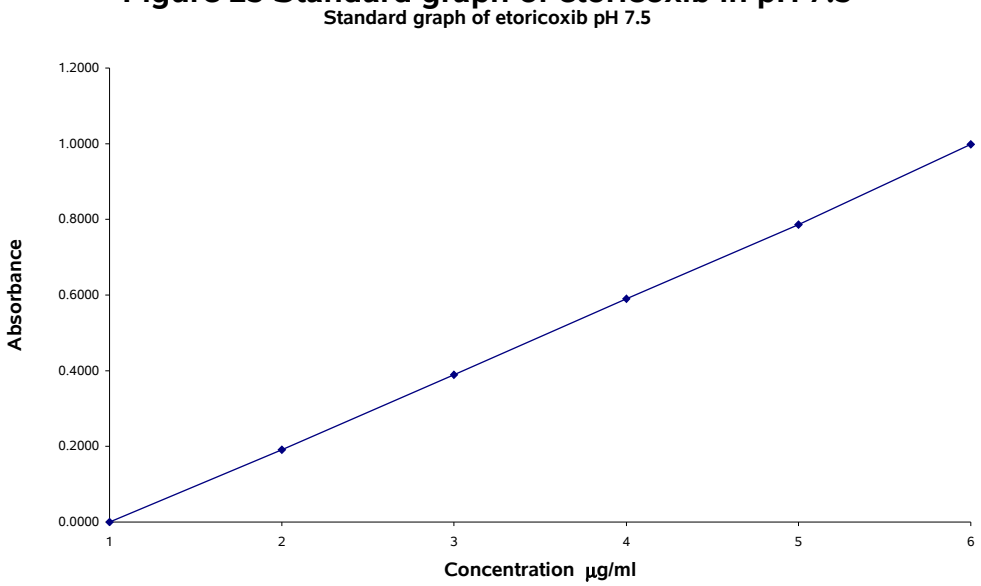


Table 10 Standard graph of etoricoxib in pH 7.5

Sl.No	Concentration in µg/ml	Absorbance at 284 nm
0	0	0.000
1	5	0.2012
2	10	0.3922
3	15	0.6025
4	20	0.7917
5	25	0.9612

Figure 25 Standard graph of etoricoxib in pH 7.5



MATERIALS AND EQUIPMENTS

MATERIALS	COMPANY/SOURCE
Etoricoxib	Anglo French Drugs and Industries Pvt.Ltd
Cellulose Acetate	Loba chemie Pvt.Ltd
Eudragit S100	Rohm Pharma, Darmstadt Germany, (Degussa polymers, Mumbai.)
Acetone	Qualigens Fine Chemicals
Liquid paraffin Light	Fisher Ltd
Ethanol	Jiangsu Huaxi International Trade Co.Ltd China
Methanol	Loba Chemie Pvt.Ltd
Span-80	Loba Chemie Pvt.Ltd
Sodium hydroxide	Loba Chemie Pvt.Ltd
Whatmann filter Paper no.1	Qualigens

Equipments	COMPANY/MODEL
Stirrer	Remi Motors
UV visible Spectrophotometer	JASCO –UV- 530
Scanning Electron Microscope	JSM 6400
Digital balance	Denver Instruments XP-300
Dissolution apparatus	Elecrto Lab
Vacuum pump	Gelmen Series
Fourier Transform Infra Red-Spectrophotometer	JASCO FT IR 410

METHOD OF PREPARATION

Microspheres of etoricoxib are prepared by solvent evaporation method by using two different polymers like, cellulose acetate and Eudragit S 100 to achieve colon specific drug delivery. The preparation is done by using different drug: polymer ratios like **1:1, 2:1, 4:1** which are called as core microspheres. These core microspheres are again coated with eudragit S 100 at different ratios to study the controlled release of the drug in colon.

MICROENCAPSULATION TECHNIQUE[58]

By solvent evaporation technique

Preparation of cellulose acetate cores containing the drug.

Etoricoxib was dissolved in the polymer solution containing the core polymer i.e., cellulose acetate in acetone at (1% w/v) with different drug: polymer ratios like **1:1, 2:1 and 4:1.** The polymer and drug containing the solvent is emulsified into an immiscible lipophilic phase, with mineral oil, in the presence of oil - soluble surfactant such as span-80. About 10ml of acetone was added to the external phase to produce a stable o/o emulsion.

Procedures

70 ml of liquid paraffin containing 1% w/w of span -80 is kept in a variable speed propeller stirrer for 2000 rpm. The drug-polymer solution in acetone is added by thin drops into the oil phase and the system is maintained for stirring 3 hrs. About 10ml of acetone was added to the system. After 3 hrs, the formed microspheres, were separated and washed with n-hexane and dried for 48 hrs in vacuum desiccator.

The above procedure was used, for microencapsulation of drug loaded cellulose acetate cores with the polymer. The cores were suspended in 5 ml of ethanolic solution of eudragit S 100 (10% w/v) in different ratios of cores like 1:1, 2:1, 4:1 with core: coat ratios 1:2.5, 1:5 and 1:7.5 respectively. The above polymer solution was emulsified in liquid paraffin containing span 80 (1% w/w). About 5 ml of ethanol was added in to the external phase .The system is maintained in variable speed propeller at 2000 rpm for 3 hrs. The formed microcapsules were separated and washed with n-hexane and dried for 48 hrs in vacuum desiccators.

Table 11 Drug and polymer at different ratios

Code	Drug :Polymer (cores)
Cr_1	1:1
Cr_2	2:1
Cr_3	4:1

Code	Core (Drug: Polymer)	Core : Coat
Ct_1 Ct_2 Ct_3	1:1	1:2.5
		1:50
		1:7.5
Ct_4 Ct_5 Ct_6	2:1	1:2.5
		1:50
		1:7.5
Ct_7 Ct_8 Ct_9	4:1	1:2.5
		1:50
		1:7.5

EVALUATION OF ETORICOXIB MICROSPHERES

1. **Compatibility studies by using FT-IR**
2. **Thin - layer chromatography**
3. **Drug content uniformity**
4. **Scanning electron microscopy**
5. **In vitro dissolution studies**

A. QUALITATIVE ANALYSIS BY INFRA-RED SPECTROSCOPY

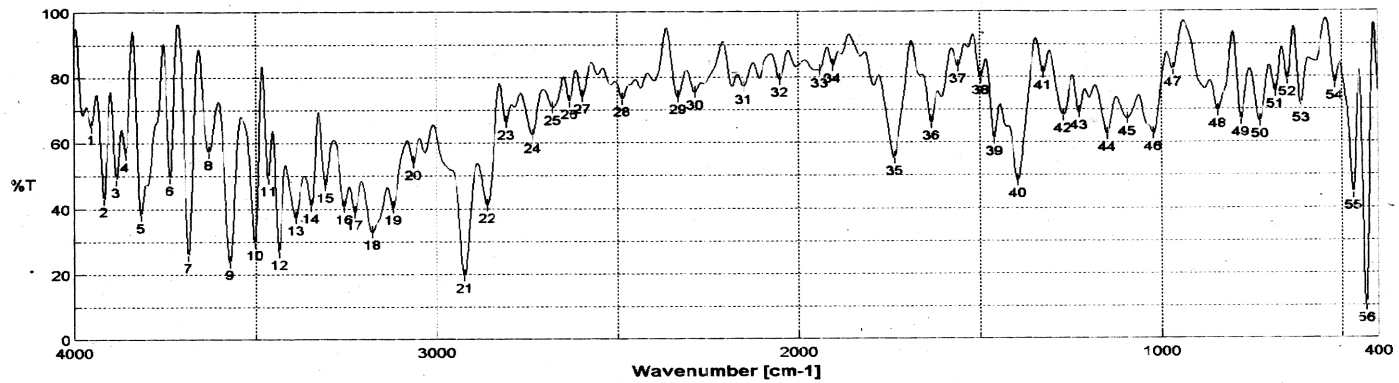
Compatibility Studies

Microspheres prepared at different ratios were mixed with suitable quantity of potassium bromide .About 100mg of the mixture was compressed to form transparent pellet in a hydraulic press at 15 tons pressure. The pellet was scanned at 4000 to 400 cm^{-1} in a FTIR spectrophotometer. The microspheres were preserved in an air tight container and the spectra were recorded at 1 and 2 months interval.

There was no appearance on disappearance of any characteristic peaks, which confirmed the absence of any chemical interaction between drug and polymer.

Similarly IR spectra of the drug loaded cores were also recorded.

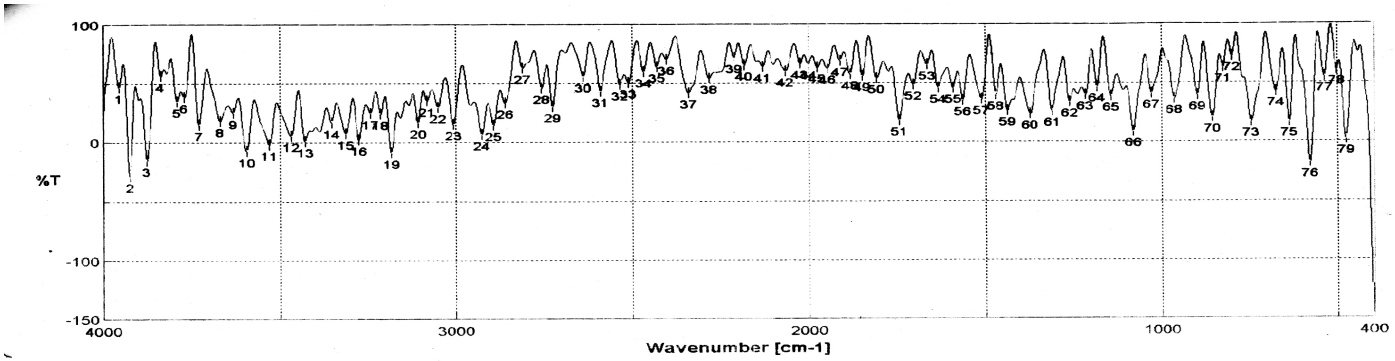
Figure 26 IR Spectra of Cellulose acetate cores at ratio 1:1



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	64	Scanning Speed	2 mm/sec
Date/Time	12/14/2007 3:01PM	Update	12/17/2007 11:49AM
Operator	C.Geetha		
File Name	H		
Sample Name	F		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3952.39	65.0654	2	3917.68	43.0448	3	3883.93	49.0669	4	3858.86	56.8362	5	3816.44	38.1298
6	3736.4	49.4796	7	3685.3	25.9655	8	3628.41	57.3302	9	3571.52	23.7525	10	3503.06	29.771
11	3465.46	49.4035	12	3436.53	26.8058	13	3390.24	37.3315	14	3346.85	41.0601	15	3308.28	47.2675
16	3255.25	40.6887	17	3225.36	38.9875	18	3178.11	32.8251	19	3119.3	40.4158	20	3064.33	54.0781
21	2924.52	19.558	22	2860.88	41.1195	23	2808.81	66.3658	24	2735.53	62.3704	25	2679.6	70.8834
26	2632.36	72.624	27	2597.64	74.2482	28	2486.76	73.4467	29	2333.44	74.1029	30	2287.16	75.3491
31	2151.2	77.1403	32	2050.92	79.2262	33	1941.97	82.0804	34	1905.33	83.6069	35	1736.58	55.1931
36	1633.41	65.9364	37	1559.17	83.3179	38	1497.45	79.8933	39	1459.85	61.0982	40	1395.25	48.3583
41	1323.89	81.3505	42	1267.97	68.2784	43	1225.54	69.051	44	1147.44	62.5034	45	1092.48	67.2152
46	1021.12	62.7331	47	967.126	82.3073	48	841.776	69.5828	49	777.172	66.916	50	726.068	66.2682
51	683.642	75.4116	52	649.893	79.0905	53	613.252	71.1833	54	519.722	78.0239	55	468.617	23.5412
56	433.905	9.92998										60	1372.1	

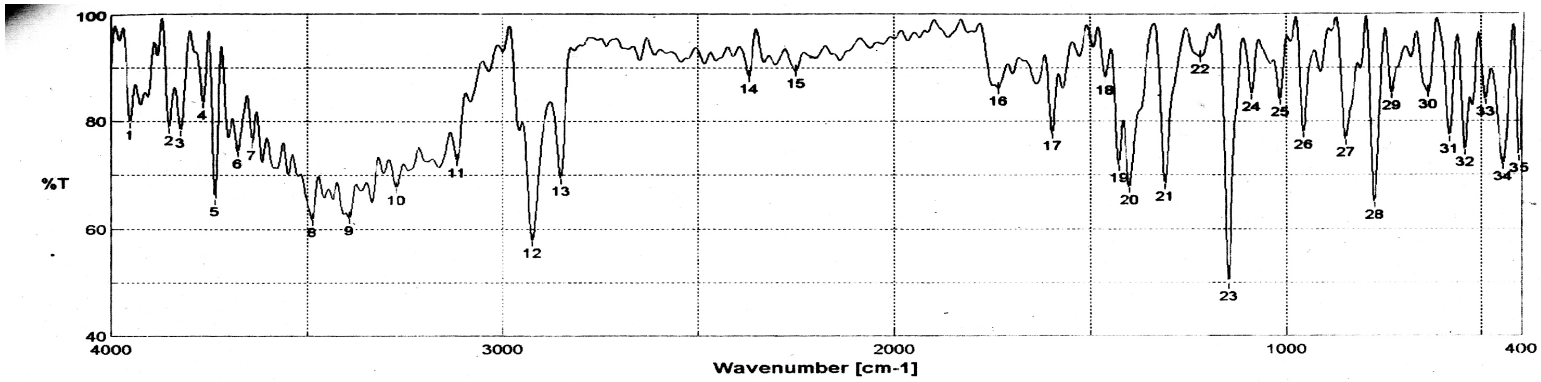
Figure 27 IR Spectra of Cellulose acetate cores at ratio 2:1



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	128	Scanning Speed	2 mm/sec
Date/Time	12/14/2007 3:08PM	Update	12/15/2007 10:19AM
Operator	C.Geetha		
File Name	I		
Sample Name	G		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3956.25	47.0722	2	3925.39	-28.4622	3	3877.18	-14.9101	4	3837.65	56.4203	5	3791.37	34.8114
6	3770.15	38.3478	7	3729.66	15.1249	8	3669.87	18.1357	9	3632.27	25.2664	10	3594.66	-7.31027
11	3531.02	-1.76518	12	3470.28	5.58762	13	3429.78	1.17138	14	3354.57	17.01	15	3314.07	7.74931
16	3275.5	2.44342	17	3242.72	24.8718	18	3212.83	24.2193	19	3182.93	-8.53146	20	3107.72	16.7233
21	3082.65	35.0818	22	3051.8	29.7292	23	3007.44	15.348	24	2927.41	6.60816	25	2893.66	14.5762
26	2860.88	33.4566	27	2810.74	63.0897	28	2757.71	45.7887	29	2726.85	30.2347	30	2640.07	55.7378
31	2590.9	43.3526	32	2535.93	48.7309	33	2511.83	50.4783	34	2467.47	59.9029	35	2430.83	63.7729
36	2403.83	70.5103	37	2341.16	41.5473	38	2283.3	54.1038	39	2211.95	71.6129	40	2183.02	65.3593
41	2129.99	64.0209	42	2065.39	60.4871	43	2022.96	66.656	44	1999.82	66.2471	45	1974.75	63.4152
46	1945.82	62.3373	47	1911.11	68.9975	48	1882.18	57.3186	49	1847.47	56.0031	50	1807.94	54.0327
51	1744.3	18.2276	52	1703.8	48.7828	53	1664.27	66.0255	54	1633.41	46.1604	55	1590.99	45.9344
56	1563.02	35.3299	57	1509.99	36.2914	58	1469.49	39.7543	59	1436.71	26.4514	60	1372.1	23.5412

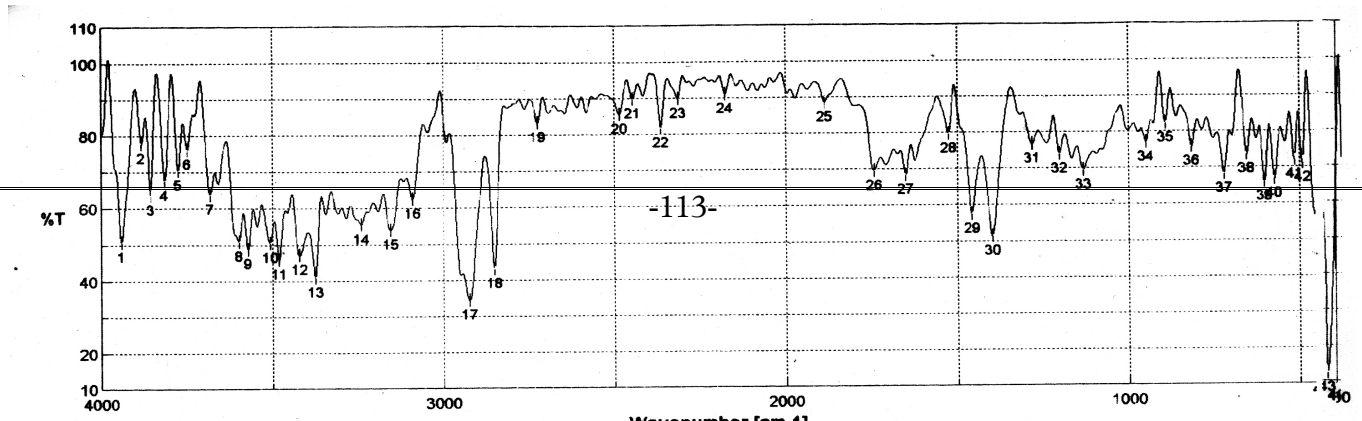
Figure 28 IR Spectra of Cellulose acetate cores at ratio 4:1

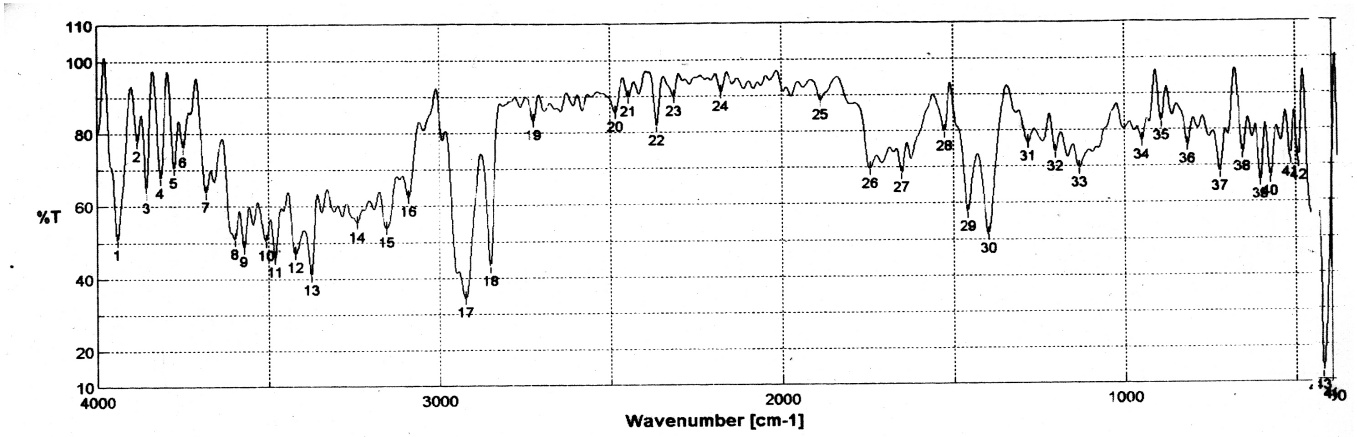


Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	16	Scanning Speed	2 mm/sec
Date/Time	12/14/2007 3:14PM	Update	12/15/2007 10:25AM
Operator	C.Geetha		
File Name	J		
Sample Name	H		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3951.43	79.8612	2	3852.11	78.862	3	3823.19	78.3289	4	3765.33	83.6373	5	3734.48	65.6559
6	3677.59	74.4455	7	3640.95	76.0202	8	3487.63	61.7142	9	3392.17	82.0849	10	3271.64	67.7633
11	3117.37	72.8529	12	2924.52	57.8801	13	2853.17	69.3935	14	2370.09	88.4438	15	2251.49	89.4897
16	1733.69	86.1884	17	1596.77	77.7861	18	1460.81	88.1644	19	1427.07	71.7843	20	1400.07	67.7647
21	1308.46	68.4169	22	1218.79	92.157	23	1147.44	49.7809	24	1087.66	85.1161	25	1015.34	84.1907
26	955.555	78.0385	27	847.561	76.595	28	774.279	64.964	29	729.925	85.2686	30	637.358	85.4241
31	581.433	77.1597	32	541.899	74.685	33	488.866	84.1553	34	444.512	72.0629	35	404.978	73.5768

Figure 29 IR Spectra of Etoricoxib microspheres of 1:1 cores coated with 1:5 of eudragit S 100

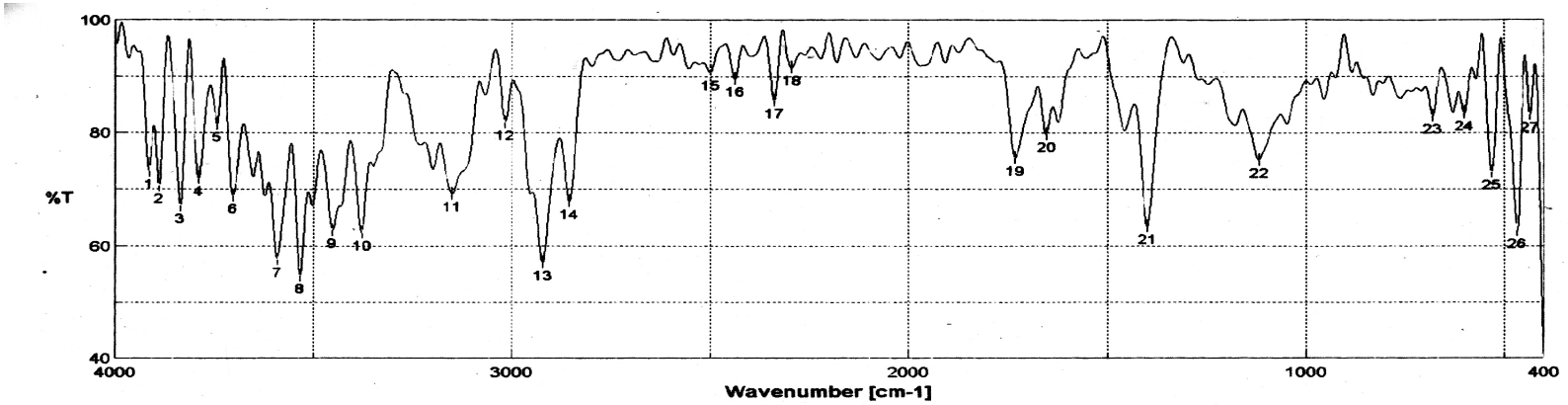




Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	32	Scanning Speed	2 mm/sec
Date/Time	12/14/2007 3:25PM	Update	12/15/2007 10:31AM
Operator	C.Geetha		
File Name	L		
Sample Name	J		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3940.82	50.6654	2	3882	77.8373	3	3855.01	63.6835	4	3813.54	67.7097	5	3774.01	70.4697
6	3747.98	76.1208	7	3681.44	63.7579	8	3598.52	50.8999	9	3570.56	48.786	10	3507.88	50.5381
11	3479.92	45.7833	12	3420.14	47.1031	13	3374.82	40.8589	14	3241.75	55.5408	15	3154.97	53.9851
16	3091.33	62.4988	17	2925.48	34.3682	18	2852.2	43.1055	19	2723.96	83.303	20	2485.79	85.594
21	2447.22	89.884	22	2365.26	81.7683	23	2316.09	89.8745	24	2177.24	91.0914	25	1886.04	88.5449
26	1743.33	69.6104	27	1650.77	68.3375	28	1525.42	79.7364	29	1457.92	57.5019	30	1398.14	51.3318
31	1282.43	76.6379	32	1202.4	74.0431	33	1131.05	69.6055	34	948.806	77.0503	35	891.916	82.3446
36	814.777	75.7797	37	720.282	68.3138	38	655.679	73.545	39	602.646	65.9523	40	573.719	66.678
41	515.865	72.0163	42	491.759	71.1343	43	438.726	12.484						

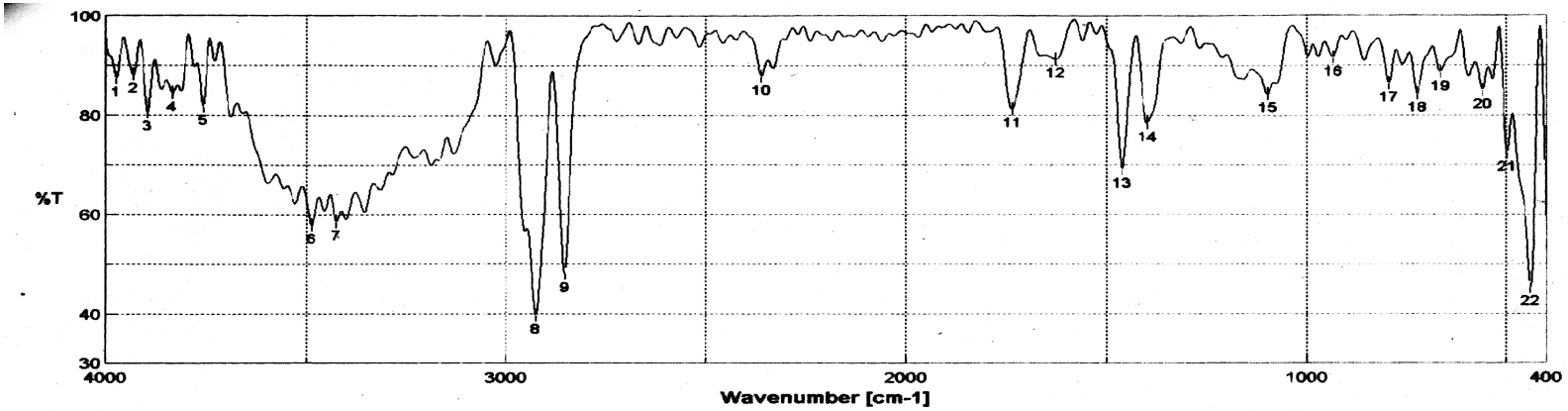
Figure 30 IR Spectra of Etoricoxib microspheres of 2:1 cores coated with 1:5 of eudragit S 100



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	16	Scanning Speed	2 mm/sec
Date/Time	12/14/2007 3:39PM	Update	12/15/2007 10:38AM
Operator	C.Geetha		
File Name	O		
Sample Name	M		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3914.79	73.3185	2	3888.75	70.7732	3	3835.72	67.2036	4	3789.44	72.0044	5	3744.12	81.571
6	3703.62	68.8939	7	3591.77	57.6675	8	3532.95	54.7753	9	3452.92	62.8704	10	3379.64	62.3746
11	3150.15	69.2874	12	3017.09	81.9581	13	2923.56	57.0843	14	2856.06	67.9106	15	2501.22	90.8379
16	2438.55	89.6376	17	2339.23	85.7995	18	2294.88	91.696	19	1732.73	75.616	20	1654.62	79.7918
21	1400.07	63.4643	22	1117.55	75.2891	23	679.785	83.034	24	600.717	83.6	25	532.257	73.1989
26	467.653	62.7414	27	434.869	83.3639									

Figure 31 IR Spectra of Etoricoxib microspheres of 4:1 cores coated with 1: 5 of eudragit S 100



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	16	Scanning Speed	2 mm/sec
Date/Time	12/14/2007 3:55PM	Update	12/15/2007 10:46AM
Operator	C.Geetha		
File Name	R		
Sample Name	P		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3972.64	87.5125	2	3931.18	88.1988	3	3895.5	80.542	4	3833.79	84.4894	5	3757.62	81.7036
6	3486.67	57.9301	7	3424.96	58.6163	8	2925.48	39.6742	9	2853.17	48.0841	10	2360.44	87.8584
11	1736.58	81.1752	12	1626.66	91.2754	13	1460.81	69.1116	14	1398.14	78.3285	15	1097.3	84.2841
16	933.378	91.6449	17	793.564	86.441	18	722.211	84.2966	19	665.321	88.6689	20	559.255	85.0163
21	497.544	72.4858	22	438.726	45.3644									

B. THIN - LAYER CHROMATOGRAPHY

The preliminary identification of Etoricoxib and also the microspheres was performed by TLC method.

Pre coated TLC plates	:	Manufactured by S.D. Fine Chem. Ltd.
Absorbent layer	:	Silica gel 60 G
Layer thickness	:	0.10 mm
Size	:	10 x 20 cm
Separation Technique	:	Ascending
Mobile phase	:	Chloroform: methanol: Toluene in the ratio 1:2:1:
Chamber saturation	:	The Chamber was lined on three sides and saturated for 30 minutes with the above mobile phase.
Preparation of test sample	:	Microspheres were crushed and extracted with methanol.
Preparation of standard	:	Pure sample of Etoricoxib was dissolved in methanol.
Detection	:	Dark Violet Spot in UV
Rf	:	Distance traveled by the solute spot / Distance traveled by the solvent front

Rf. Values are shown in table

Table 12 Rf. Values of etoricoxib microspheres

Sl.No.	Name of the Sample	Color Detected	Rf Values
1	Standard Drug	Violet	0.606
2.	Test Drug	Violet	0.595

C. DRUG CONTENT UNIFORMITY

Microspheres containing 10 mg equivalent weight of etoricoxib was accurately weighed and dissolved in 2 ml of acetone. Acetone was evaporated by keeping in mantle at low temperature. The residue left behind is dissolved in methanol and the volume made up to 10 ml. The above solution was kept for 1 hour. The contents were filtered. The absorbance of the filtrate was measured at 284 nm by using UV spectrophotometer.

Microspheres were also extracted with 10ml of 0.1 N HCl. After 12 hours, the solution was filtered using Whatmann filter No.1. From this 1 ml was diluted to 5 ml with the same 0.1 N HCl and the absorbance of the filtrate was measured against the buffer as a blank at 284 nm using UV visible spectrophotometer .Similar procedure was followed for the extraction with phosphate buffer of pH 7.5.

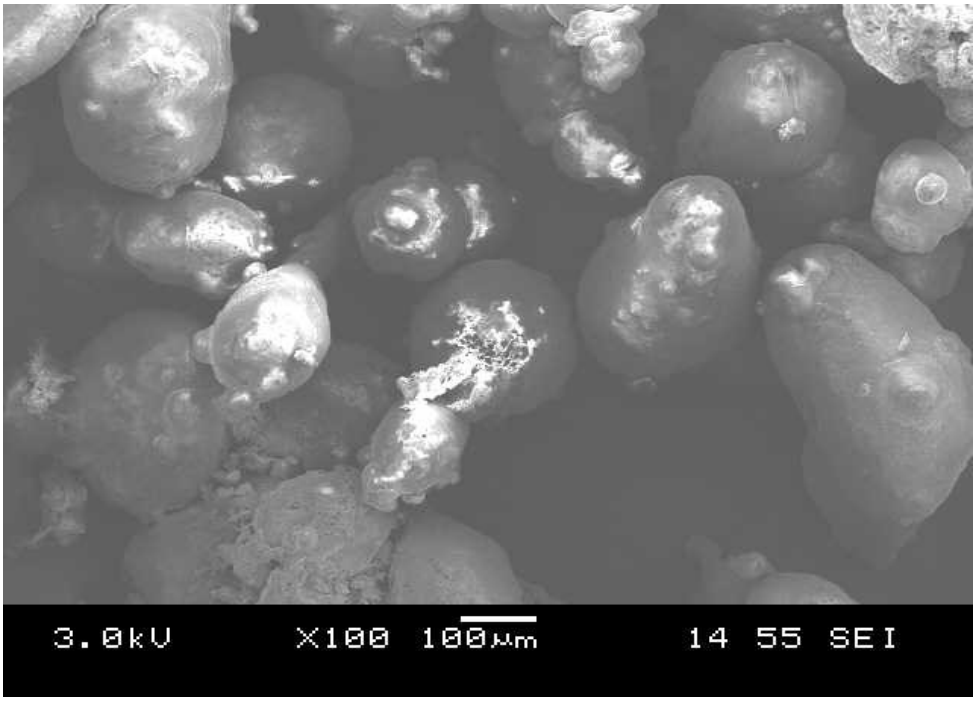
Table 13 Drug Content uniformity

Formulations code	Cores(Drug: Polymer)	Core : Coat	Drug Content (mg)
Ct_1 Ct_2 Ct_3	1:1	1:2.5	9.3
		1:5	9.5
		1:7.5	9.58
Ct_4 Ct_5 Ct_6	2:1	1:2.5	8.9
		1:5	9.4
		1:7.5	9.54
Ct_7 Ct_8 Ct_9	4:1	1:2.5	9.6
		1:5	9.52
		1:7.5	9.0

D. SCANNING ELECTRON MICROSCOPY

The Surface morphology and internal structure of the products was observed by a scanning electron microscope.Microspheres were fixed on an aluminum stubs using a double sided tube , sputter coated with gold to make the surface conductive and examined under microscope .SEM photographs were taken by using JSM 6400 Scanning Electron Microscope at the 120x magnification at room temperature . SEM photographs are shown in figure.

Figure 32 SCANNING ELECTRON MICROSCOPY OF CELLULOSE ACETATE CORES



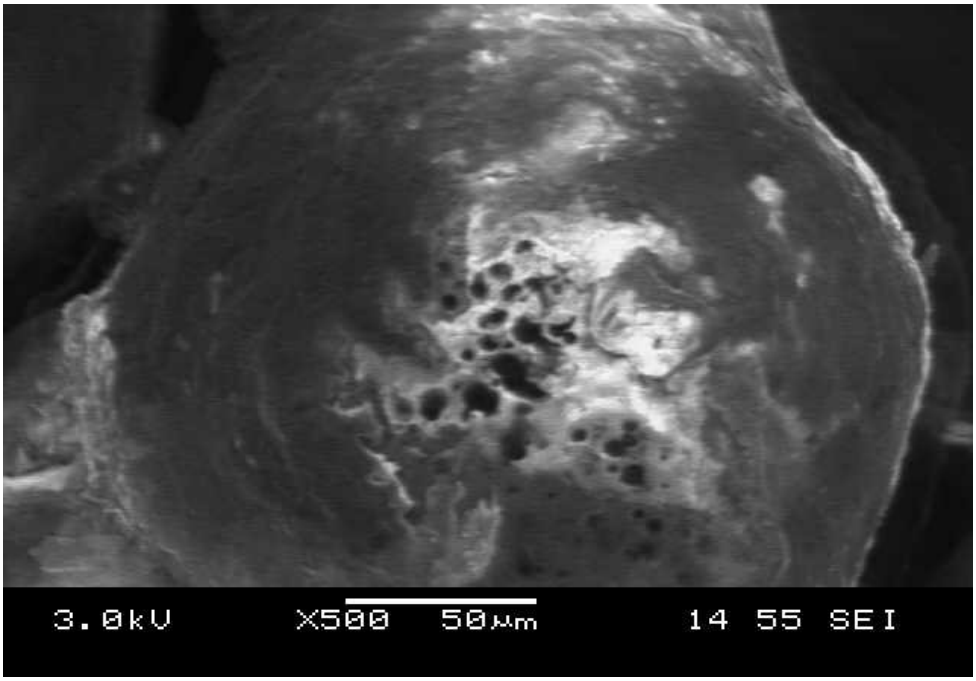
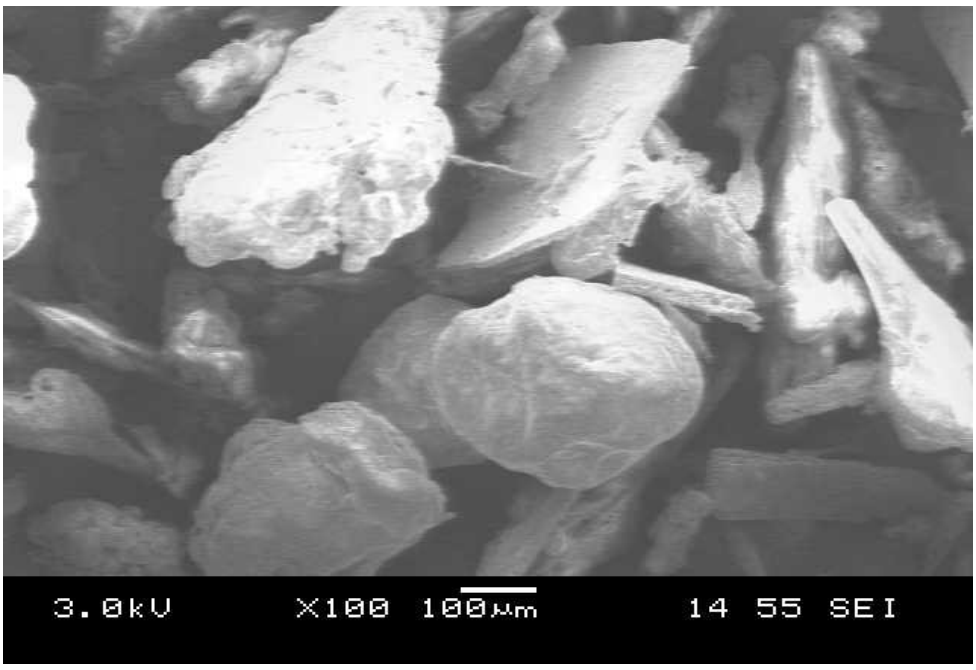
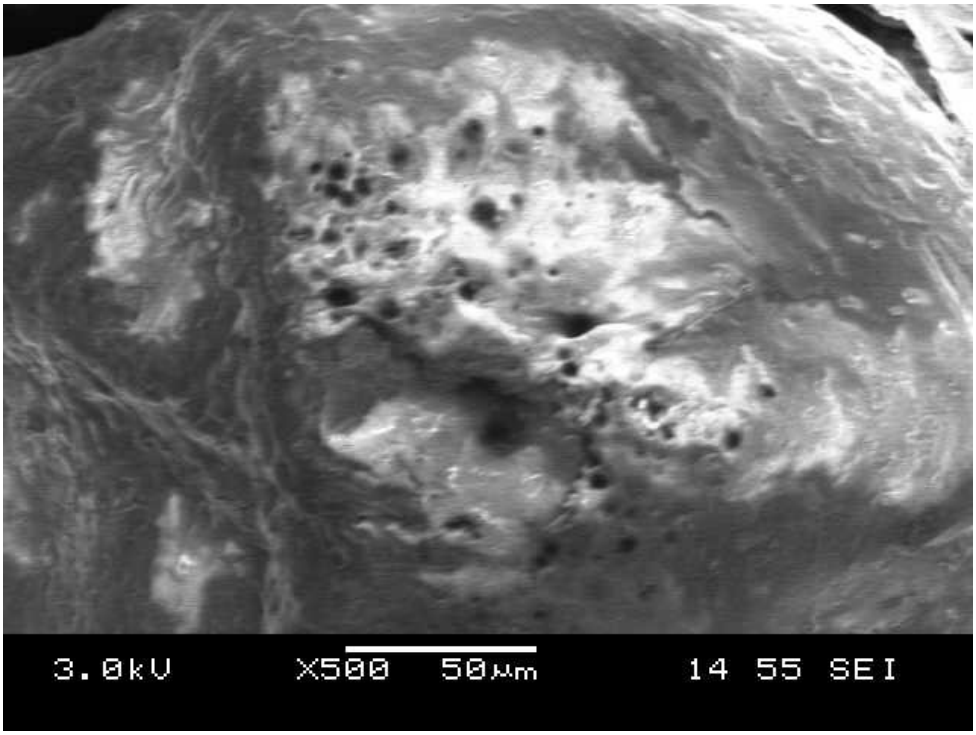


Figure 33 SCANNING ELECTRON MICROSCOPY OF ETORICOXIB MICROCAPSULES COATED WITH EUDRAGIT S 100





E. IN-VITRO DISSOLUTION STUDIES [58, 59]

The microspheres were evaluated for their integrity in the physiological environment of stomach and small intestine under conditions mimicking mouth to colon transit.

Dissolution studies of eudragit micro capsules were carried out in triplicate using USP XIII dissolution rate test Apparatus

The microspheres were tested for drug release for 2 hrs in 0.1 N HCl (900ml) as the average gastric emptying time is almost 2 hrs. Weighed quantities of micro capsules were loaded into the basket of dissolution apparatus containing 0.1 N HCl.

Then the dissolution medium was replaced with mixed phosphate buffer pH 7.5 (900 ml) and tested for drug release till the end of the test i.e. for 10 hours .The temperature of the dissolution medium was maintained at 37±0.5˚C with a stirring speed of 100 rpm .Samples were withdrawn every hour filtered through Whatmann filter paper, diluted and analyzed spectrophotometrically.

The dissolution studies of the cellulose acetate cores were also performed under same set of experimental conditions.

Table 14 Dissolution studies of cellulose acetate cores

Sl.No.	Time in hours	Percent of Drug Release from Cores		
		1:1	2:1	4:1
1	0	0.00	0.00	0.00
2	1	9.56	10.25	11.36
3	2	11.25	12.15	13.45
4	3	20.62	24.38	28.12
5	4	26.25	28.12	33.75
6	5	31.88	33.75	37.50
7	6	33.75	37.50	41.25
8	7	37.50	46.87	46.87
9	8	46.87	50.62	51.15
10	9	52.50	54.38	58.12
11	10	56.25	58.13	61.88
12	11	59.16	62.89	69.39
13	12	63.75	66.33	72.44

Figure 34 Dissolution studies of etoricoxib cores with cellulose acetate

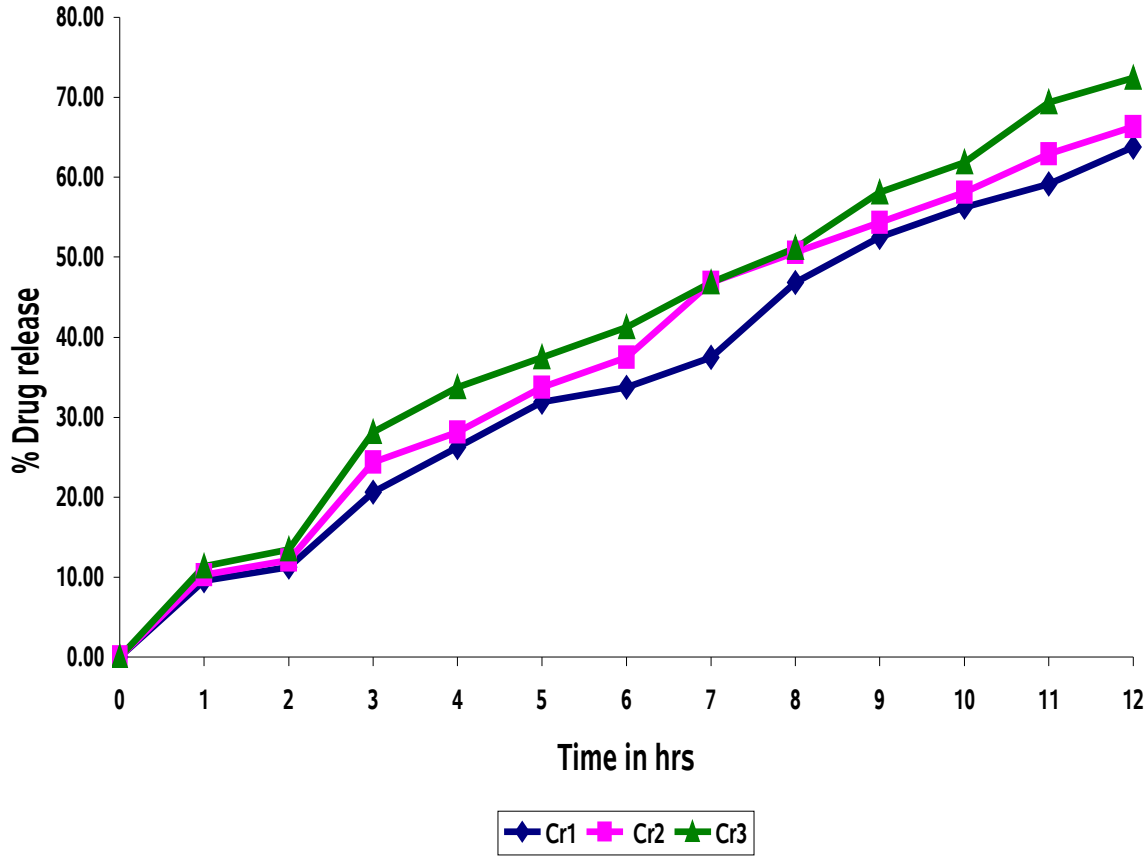

80.00
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
% Drug release
0
1
2
3
4
5
6
7
8
9
10
11
12
Time in hrs
Cr1
Cr2
Cr3

Table 15 Dissolution studies of Etoricoxib microspheres of 1:1 cores coated with Eudragit S 100 at different ratios

Sl.No.	Time in hours	Percent of Drug Release from microspheres		
		1:2.5 (Ct_1)	1:5 (Ct_2)	1:7.5(Ct_3)
1	0	0.00	0.00	0.00
2	1	7.22	8.34	10.01
3	2	7.99	9.06	10.78
4	3	20.62	24.38	28.12
5	4	24.38	30.67	39.37
6	5	30.35	36.65	37.50
7	6	33.22	41.56	45.17
8	7	37.50	46.87	50.62
9	8	43.12	50.67	54.37
10	9	45.33	51.15	55.89
11	10	48.35	52.12	56.78
12	11	51.54	54.56	58.13
13	12	53.78	58.12	61.69

Figure 35 Dissolution studies of Etoricoxib microspheres of 1:1 cores coated with Eudragit S 100 at different ratios

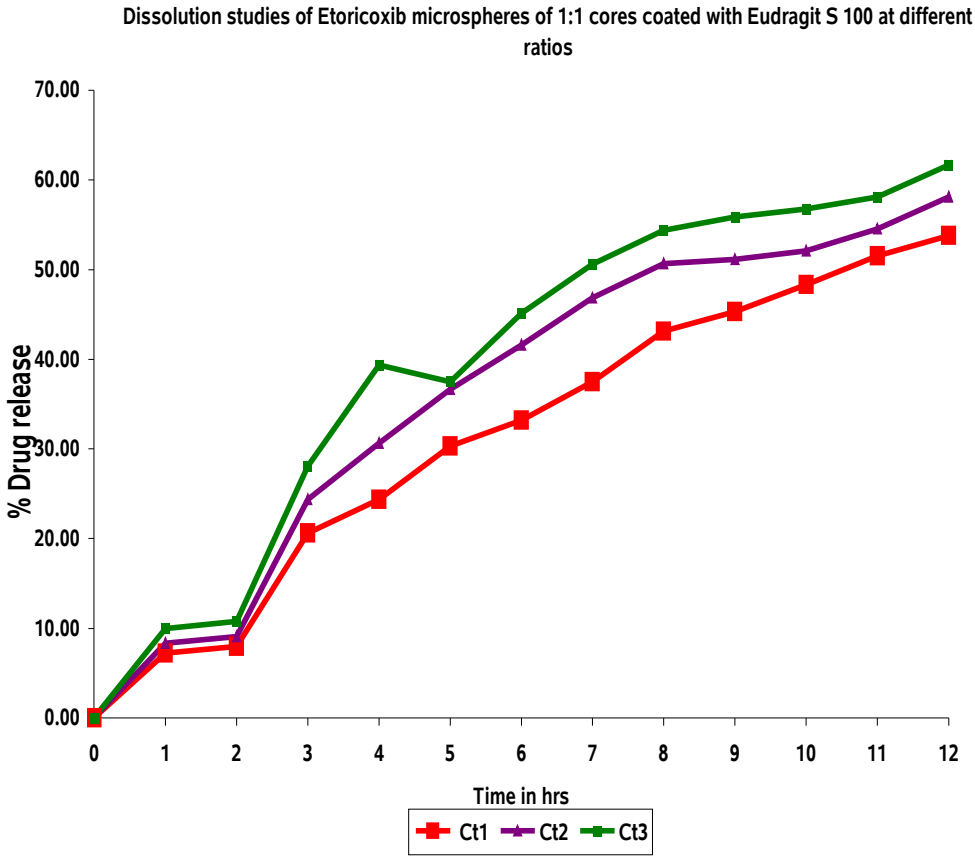


Table 16 Dissolution studies of Etoricoxib microspheres of 2:1 cores coated with Eudragit S 100 at different ratios

Sl.No.	Time in hours	Percent of Drug Release from microspheres		
		1:2.5(Ct_4)	1:5(Ct_5)	1:7.5(Ct_6)
1	0	0.00	0.00	0.00
2	1	8.05	9.11	10.56
3	2	9.67	10.45	11.89
4	3	21.33	26.13	30.23
5	4	26.12	32.09	34.67
6	5	33.35	39.12	40.99
7	6	35.12	43.16	45.84
8	7	40.67	49.90	51.34
9	8	45.89	53.07	56.44
10	9	48.45	56.14	58.12
11	10	50.67	59.77	61.98
12	11	54.05	60.68	63.75
13	12	57.12	61.66	65.62

Figure 36 Dissolution studies of Etoricoxib microspheres of 2:1 cores coated with Eudragit S 100 at different ratios

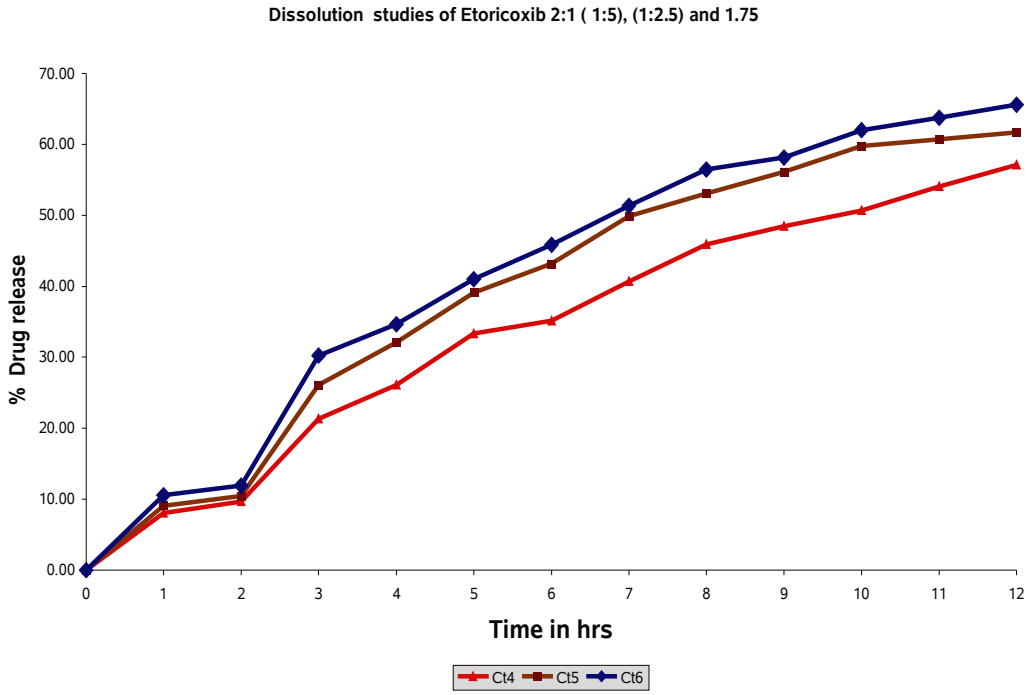
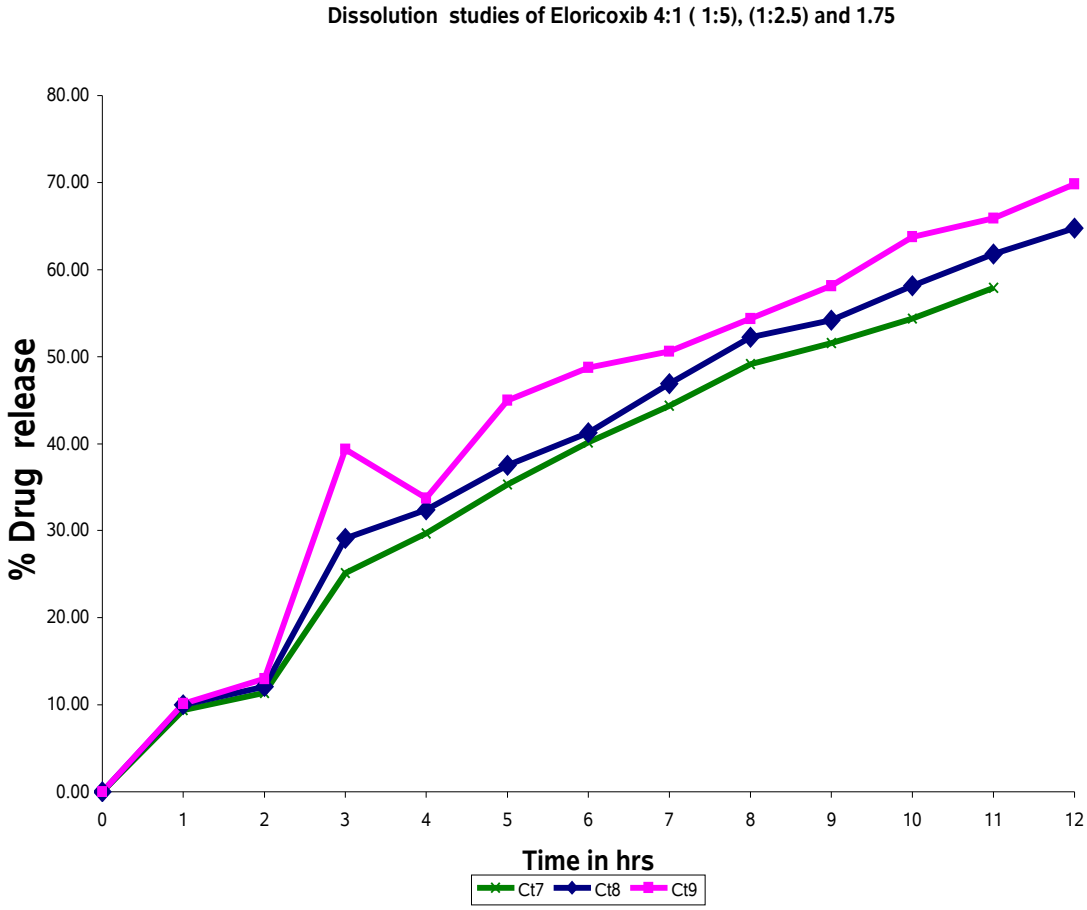


Table 17 Dissolution studies of Etoricoxib microspheres of 4:1 cores coated with Eudragit S 100 at different ratios

Sl.No.	Time in hours	Percent of Drug Release from microspheres		
		1:2.5(Ct_7)	1:5(Ct_8)	1:7.5(Ct_9)
1	0	0.00	0.00	0.00
2	1	9.37	9.99	10.11
3	2	11.33	12.11	12.98
4	3	25.11	29.12	39.37
5	4	29.67	32.37	33.75
6	5	35.33	37.50	45.00
7	6	40.12	41.25	48.75
8	7	44.35	46.87	50.62
9	8	49.12	52.22	54.37
10	9	51.56	54.21	58.12
11	10	54.37	58.13	63.75
12	11	57.88	61.77	65.88
13	12	62.12	64.78	69.82

Figure 37 Dissolution studies of Etoricoxib microspheres of 4:1 cores coated with Eudragit S 100 at different ratios



RESULTS AND DISCUSSION

Microspheres of etoricoxib with different polymers were formulated with objective of controlled release of etoricoxib for the site specific delivery of drug to the colon.

Microencapsulation was done by solvent evaporation technique. Microspheres were prepared by using the polymers such as cellulose acetate and Eudragit S 100. Cellulose acetate cores containing the etoricoxib were prepared by emulsion solvent evaporation method, where the organic solution containing the etoricoxib and cellulose acetate in acetone was emulsified into an external oily phase of liquid paraffin. For the formation of a stable emulsion, small amount of acetone is added to the external oily phase to prevent the precipitation and also to avoid diffusion of the organic solvent to the oily phase.

The prepared microspheres were characterized for the interaction studies like, compatibility evaluation using FT-IR, TLC, Drug Content uniformity, SEM and in-vitro dissolution studies.

The preformulation studies confirmed no interaction between the drug and polymers as there is no appearance or disappearance of any characteristic peaks .The Rf values also confirms that there is no interaction between drug and polymers used. The microspheres prepared have good spherical geometry as it is clearly evidenced from scanning electron microscopic pictures. The selection of the dispersion medium is

an important factor for obtaining spherical shape of optimum size. The cores have got a rough surface due to rapid solvent evaporation and quick precipitation of cellulose acetate during the formation of an o/o emulsion.

Since liquid paraffin is used as an organic oil phase with same polymer concentration. i.e. (1% w/v cellulose acetate), there was no significant difference in the emulsion globule size.

The in-vitro release profile of cellulose acetate cores were studied in 0.1 N HCl and mixed phosphate buffer pH 7.5. The results are given in tables 14 and in figure 34 . From the figure it was found that the cores were intact at 0.1 N HCl and having the etoricoxib release of only 9.56%, 10.25% and 11.36% for 1:1, 2:1, 4:1 drug: polymer ratios respectively. But the drug release was found to be slow release phase followed by a controlled release in mixed phosphate buffer pH 7.5 with a percentage release of 63.73%, 66.33%, and 72.44% for 1:1, 2:1 and 4:1 drug: polymer ratios respectively at the 12^{th} hour.

The cellulose acetate cores were again microencapsulated with pH sensitive acrylic polymer, Eudragit S 100 which can dissolve only in above pH 7. Eudragit S 100 can protect the cellulose acetate core in the upper part of gastro intestinal tract, which could effectively control the drug at the target site.

The cellulose acetate cores were coated with different core to coat ratios like 1:2.5, 1:5 and 1:7.5 for each ratio of the cores. The prepared microspheres were subjected to in-vitro dissolution studies.

Preformulation studies were also performed with coated microspheres which confirm no interactions with the polymer and drug. The SEM photographs of the coated microspheres revealed the spherical size of the microspheres with the smooth and dense surface. The microcapsules were also subjected for drug content uniformity .There was no loss of drug during the microencapsulation.

The studies showed that microspheres exhibited pH sensitive and controlled release properties. The drug release depends on pH of the dissolution medium and cellulose acetate levels in the microspheres.

It was observed from the figure 35, figure 36 and figure 37 that there was no drug release from the formulation at 0.1 N HCl. At pH 7.5 acrylic coat dissolves and releases the cellulose acetate cores which can effectively control the drug release till 12^{th} hour. From figure 35, figure 36 and figure 37 it is shown that, the etoricoxib is getting controlled release till the end as the core: coat ratio increases, which assures to give a better therapeutic activity of the drug.

In brief, successful delivery of the drug especially to the colon requires the protection of etoricoxib from being released in the stomach and in small intestine. In this study the polymer in the form of coating by using microencapsulation was applied over etoricoxib core drug and release studies were carried under conditions mimicking from mouth to colon.

SUMMARY AND CONCLUSION

Colonic drug delivery has several therapeutic advantages. The delivery of drugs to colon is of value in the systemic disease. Etoricoxib was chosen as an experimental drug to get successful colonic delivery, a drug needed to be protected from the environment of the upper GIT and then rapidly released in colon. The study was carried out in six stages.

1. Calibration curve of etoricoxib by UV spectrophotometric method.
2. Compatability between drug and polymers was evaluated by peak matching by FTIR spectroscopic method.
3. Preparation of cellulose acetate cores containing etoricoxib.
4. Coating/microencapsulation of cellulose acetate cores with Eudragit S 100.
5. Evaluation of the above prepared microspheres by using FTIR, TLC, SEM, drug content uniformity.
6. In vitro dissolution of the formulated microspheres were evaluated in 0.1 N HCl buffer and mixed phosphate buffer pH 7.5 by using USP XIII dissolution apparatus.

The below facts derived from the work done lead to the following conclusion.

- Microcapsules are capable of releasing etoricoxib to the colon.
- The double coated microspheres are having both pH sensitive and control release properties.
- Based on the studies it can be concluded that the etoricoxib has been protected from the physiological environment of stomach and small intestine and thus capable of improving the pharmacological actions for the management of rheumatoid arthritis.

It is obvious from the above work that the study has engineered a drug delivery profile in which the drug release is controlled to a great extent and that the formulation in therapy can minimize the untoward side effect thus improving patient compliance. The industrial application of this method could be very simple and rapid.

Thus, finally etoricoxib is protected to be released in the stomach and succeeded in its release in colon which helps to improve its anti inflammatory action and protect the stomach from gastric bleeding of COX-2 inhibitors by delivering the drug directly to colon by using microencapsulation technique.

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